CLASSIFYING TUMORS AND PREDICTING RESPONSIVENESS

Cross-Reference to Related Applications

[0001] This application claims priority to United States Provisional Application No. 63/305,944, filed February 2, 2022, the entirety of which is incorporated herein by reference.

Background

[0002] Cancer is the second leading cause of death in the United States. Increasingly, immune modulating therapies, such as therapy with immune checkpoint inhibitors (ICI) are being explored as promising potential therapies for many cancers.

Summary

[0003] The present disclosure provides technologies for determining likelihood of patient responsiveness to certain therapies (e.g., for stratifying patient populations), and for treatment of cancer by administering such therapy to responsive patients and/or populations (and/or withholding such therapy and/or administering alternative therapy to non-responsive patients and/or populations), as defined herein. In particular, the present disclosure provides technologies for determining likelihood of patient responsiveness to immunomodulation therapy.

[0004] Without wishing to be bound by any particular theory, the present disclosure provides an insight that effective biomarkers for responsiveness to relevant therapy (e.g., immunomodulation therapy, and particularly ICI therapy) may be those that capture aspects of immunosurveillance, immunosuppression, and immune evasion as a tumor transitions from a proliferative to a metastatic state. Alternatively or additionally, the present disclosure provides an insight that effective biomarkers for responsiveness to immunomodulation therapy may asses one or more features of an immunological state of the tumor microenvironment (TME).

[0005] The present disclosure demonstrates, among other things, that assessment of a mesenchymal (M) gene expression signature, a mesenchymal stem-like (MSL) gene expression signature and an immunomodulatory (IM) gene expression signature can together provide an immuno-oncology score (an IO score) that is an effective biomarker for responsiveness to certain therapies (e.g. immunomodulation therapy, and particularly ICI therapy). In some embodiments, mesenchymal (M) gene expression signature, mesenchymal stem-like (MSL) gene expression signature and immunomodulatory (IM) gene

expression signature are assessed through examination of a set of genes provided herein. In some embodiments, mesenchymal (M) gene expression signature, mesenchymal stem-like (MSL) gene expression signature and immunomodulatory (IM) gene expression signature are assessed through examination of genes determined through use of a gene expression algorithm.

[0006] In some embodiments, the present disclosure provides technologies for monitoring therapy administered to a cancer patient through assessment of an IO score over time. Alternatively or additionally, the present disclosure provides methods of selecting and/or adjusting therapies administered to a cancer patient through assessment of an IO score at multiple time points. In some embodiments, the present disclosure provides methods for selectively administering one or more therapies to a cancer patient determined to have an IO score meeting a certain threshold value.

[0007] Without wishing to be bound by a particular theory, the present disclosure provides an insight that assessment of an IO score can inform selection of a particular therapy (e.g. immunomodulation therapy, and particularly ICI therapy) for administration to a patient with a malignancy or potential malignancy. In some embodiments, the present disclosure provides an insight that assessment of an IO score can inform selection of a combination of one or more therapies, either in tandem or in sequence (e.g. comprising one or more immunomodulation therapies).

[0008] The present disclosure demonstrates, among other things, development of a tumor classifier effective to distinguish between responsiveness and non-responsiveness to immunomodulation therapy. In some embodiments, the present disclosure provides an insight that a tumor classifier can be trained for use in multiple different tumor types.

[0009] Alternatively or additionally, the present disclosure permits assessment of association (*e.g.*, correlation) with classified IM, M, and/or MSL features. In some embodiments, the present disclosure permits identification and/or characterization of other parameters (*e.g.*, RNA levels, gene expression, gene mutation, protein expression, protein modification, epigenetic modification, *etc.*) for association. In some embodiments, such associated features may comprise biomarkers that may be detected (*e.g.*, measurement of presence and/or or levels). In some embodiments, such associated features may comprise a particular form (*e.g.*, variant form (*e.g.*, presence of a particular allele or mutation), modified form (*e.g.*, epigenetic modification of a gene or gene associated sequence, phosphorylation

or glycosylation of a protein, etc.), a particular one of known forms (*e.g.*, splicing forms, allelelic forms, etc.), etc.) of one or more genes or gene products. In some embodiments, technologies provided herein permit assessment of association with IM, M, and/or MSL features, which can reveal presence and/or development of biological event(s) that recommend particular therapy be used in addition or as an alternative to immunomodulation therapy.

[0010] In some embodiments, the present disclosure provides a method of characterizing a potential cancer therapy by determining that said therapy directly or indirectly correlates with IM, M, and/or MSL features. In some embodiments, the present disclosure provides a method comprising a step of detecting in a subject who is a candidate for receiving a particular therapy a biomarker established to correlate with responsiveness or non-responsiveness to the therapy.

[0011] In some embodiments, the present disclosure provides a method of treating a subject in whom a biomarker has been detected, the method comprising steps of administering immunomodulation therapy or therapy that sensitizes to immunomodulation therapy if the therapy has been correlated with IM status and administering alternative therapy if the biomarker has been correlated with M or MSL subtype.

[0012] In some embodiments, the present disclosure provides a method of treating a subject in whom a biomarker has been detected, the method comprising steps of administering therapy that has been correlated with IM status if the biomarker has also been so correlated and administering therapy that has been correlated with M or MSL subtype if the therapy has also been so correlated.

[0013] In some embodiments, mesenchymal (M) gene expression signature, mesenchymal stem-like (MSL) gene expression signature and/or immunomodulatory (IM) gene expression signatures as provided here, and/or models or representations of tumor subtype and/or are used to establish and/or characterize (e.g., validate) biomarkers of tumor subtype or status (i.e., of IM, M, or MSL character), and/or of responsiveness to particular therapy, for example by demonstrating correlation with a provided gene expression signature and/or with a result (e.g., a heat map) of its application to tissue analysis.

[0014] Still further, by demonstrating effectiveness of provided technologies at classifying tumor subtype, status and/or responsiveness, the present disclosure provides

technologies that permit investigation and/or interpretation of data such as clinical and/or cell line data, including relevant to development of resistance to one or more particular therapies (e.g., ICI therapy) and/or emergence of additional targets for therapy. Thus, in some embodiments, the present disclosure provides technologies for identifying and/or characterizing therapeutic targets, for selecting, administering and/or adjusting therapeutic regimens (e.g., to address or anticipate developing resistance and/or emerging target(s) in a particular subject or set of subjects.

[0015] Advantages of certain embodiments of provided technologies include that such assessment may be of data inputs from any of a variety of platforms; as documented herein, strategies provided by the present disclosure can provide an effective IO score biomarker independent of data input source.

Brief Description of the Drawings

[0016] **Figure 1**: Common Immune Checkpoint Pathways and FDA-Approved ICIs. Figure adapted from Hui *et al.*, "Immune checkpoint inhibitors" *J. Cell Biol.* 218, 2019, incorporated herein by reference in its entirety. Artwork by Neil Smith (nel@neilsmithillustration.co.uk).

[0017] **Figure 2**: Schematic of chimeric antigen receptor (CAR) structure, adapted from Feins et al *et al.*, "An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer", *Am J Hematol.* 94, 2019, incorporated herein by reference in its entirety.

[0018] **Figure 3**: Major types of neoantigen vaccines, adapted from Peng *et al.*, "Neoantigen vaccine: an emerging tumor immunotherapy", *Mol. Cancer*, 18, 2019, incorporated herein by reference in its entirety.

[0019] **Figure 4**: Mechanisms of Rescue of CAR T cell Exhaustion with Checkpoint Blockade, adapted from Grosser *et al.*, "Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors", *Cancer Cell*, 36, 2019, incorporated herein by reference in its entirety.

[0020] **Figure 5**: Pathways interfering with PD-1 signaling, adapted from Langdon *et al.*, "Combination of dual mTORC1/2 inhibition and immune-checkpoint blockade potentiates anti-tumour immunity", *Oncoimmunology*, 7, 2018, incorporated herein by reference in its entirety.

[0021] **Figure 6**: Gene selection process for building the 27-gene immuno-oncology algorithm. Gene set resulted from data set normalization, batch correction, gene set enrichment analysis, and elastic net modeling.

[0022] **Figure 7**: Overview of IO score as a measure of the TME state.

[0023] **Figure 8**: Mapping of IO score against gene signatures for bladder cancer data

[0024] **Figure 9**: Association of IO scoring with gene signature classifications

[0025] **Figure 10**: Placement of the 27 IO scores relative to the TME and identification of pathways associated with certain metagenes

[0026] **Figure 11**: Confirmation of IO scoring threshold accuracy

[0027] **Figure 12**: IO scoring as predictor of overall survival rates for bladder cancer ICI therapy trial.

[0028] **Figure 13**: Mapping of gene expression and compound sensitivity in relation to subtypes with training set of cell lines.

[0029] **Figure 14**: Mapping of gene expression and compound sensitivity in relation to subtypes with test set of cell lines.

[0030] **Figure 15**: Correlation of immune signatures (red is positive correlation, blue is negative correlation).

[0031] **Figure 16**: Mapping of gene expression and immune signatures in relation to subtypes for lung adenocarcinoma training data set.

[0032] **Figure 17**: Mapping of gene expression and immune signatures in relation to subtypes for lung squamous cell training data set.

[0033] **Figure 18**: Mapping of gene expression and immune signatures in relation to subtypes for lung adenocarcinoma test data set.

[0034] **Figure 19**: Mapping of gene expression and immune signatures in relation to subtypes for lung squamous cell carcinoma test data set.

[0035] **Figure 20A**: Correlation of miRNA expression to DTIO binary call for pre-miRNA validation set; **Figure 20B:** pre-miRNA test set; **Figure 20C:** mature miRNA validation set; and **Figure 20D**: mature miRNA test set.

[0036] **Figure 21**: Representation of sets of co-expressed genes across fifteen different tumor types and resulting immune infiltrate signatures.

[0037] **Figure 22**: Comparison of immune network signatures to ImmGen signatures.

[0038] **Figure 23**: Comparison of immune network signatures to xCell signatures.

[0039] **Figure 24A**: Mapping of gene expression and immune signatures in relation to subtypes for breast test data set; **Figure 24B**: for lung adenocarcinoma training data set; **Figure 24C**: for lung squamous cell carcinoma training data set; **Figure 24D**: for colon carcinoma test data set; and **Figure 24E**: for bladder carcinoma test data set;

[0040] **Figure 25A**: Mapping of gene expression and immune signatures in relation to subtypes for TCGA training set; **Figure 25B**: for TCGA test set; and **Figure 25C**: for both training and test set.

[0041] **Figure 26A**: Distribution of immune network signatures in relation to IM, M, and MSL subtypes for lymphoid training set; **Figure 26B**: for myeloid training set; **Figure 26C**: for lymphoid test set; **Figure 26D**: for myeloid test set; **Figure 26E**: for lympohid training and test sets; **Figure 26F**: for myeloid training and test sets.

[0042] **Figure 27A**: Kaplan-Meier plots of patient survival for patients for network B-cell signature for IMVIgor cohort; **Figure 26B**: for network non-B lymphoid signature for IMVIgor cohort; **Figure 27C**: for network B-cell signature for UNC bladder samples; **Figure 27D**: for network non-B lymphoid signature for UNC bladder samples.

Definitions

[0043] ***About:*** The term "about", when used herein in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by "about" in that context. For example, in some embodiments, the term "about" may encompass a range of values that within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

[0044] ***Administration***: As used herein, the term "administration" refers to the administration of a composition to a subject or system (e.g., to a cell, organ, tissue, organism, or relevant component or set of components thereof). Those of ordinary skill will appreciate that route of administration may vary depending, for example, on the subject or

system to which the composition is being administered, the nature of the composition, the purpose of the administration, etc. For example, in certain embodiments, administration to an animal subject (e.g., to a human) may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal and/or vitreal. In some embodiments, administration may involve intermittent dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time.

[0045] ***Agent*** : In general, the term "agent", as used herein, is used to refer to an entity (e.g., for example, a lipid, metal, nucleic acid, polypeptide, polysaccharide, small molecule, etc, or complex, combination, mixture or system [e.g., cell, tissue, organism] thereof), or phenomenon (e.g., heat, electric current or field, magnetic force or field, etc). In appropriate circumstances, as will be clear from context to those skilled in the art, the term may be utilized to refer to an entity that is or comprises a cell or organism, or a fraction, extract, or component thereof. Alternatively or additionally, as context will make clear, the term may be used to refer to a natural product in that it is found in and/or is obtained from nature. In some instances, again as will be clear from context, the term may be used to refer to one or more entities that is man-made in that it is designed, engineered, and/or produced through action of the hand of man and/or is not found in nature. In some embodiments, an agent may be utilized in isolated or pure form; in some embodiments, an agent may be utilized in crude form. In some embodiments, potential agents may be provided as collections or libraries, for example that may be screened to identify or characterize active agents within them. In some cases, the term "agent" may refer to a compound or entity that is or comprises a polymer; in some cases, the term may refer to a compound or entity that comprises one or more polymeric moieties. In some embodiments, the term "agent" may refer to a compound or entity that is not a polymer and/or is substantially free of any polymer and/or of one or more particular polymeric moieties. In some embodiments, the term may refer to a compound or entity that lacks or is substantially free of any polymeric moiety.

[0046] ***Agonist***: Those skilled in the art will appreciate that the term "agonist" may be used to refer to an agent, condition, or event whose presence, level, degree, type, or form

correlates with increased level or activity of another agent (i.e., the agonized agent or the target agent). In general, an agonist may be or include an agent of any chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or any other entity that shows the relevant activating activity. In some embodiments, an agonist may be direct (in which case it exerts its influence directly upon its target); in some embodiments, an agonist may be indirect (in which case it exerts its influence by other than binding to its target; e.g., by interacting with a regulator of the target, so that level or activity of the target is altered).

[0047] ***Agonist Therapy***: The term "agonist therapy", as used herein, refers to administration of an agonist that agonizes a particular target of interest to achieve a desired therapeutic effect. In some embodiments, agonist therapy involves administering a single dose of an agonist. In some embodiments, agonist therapy involves administering multiple doses of an agonist. In some embodiments, agonist therapy involves administering an agonist according to a dosing regimen known or expected to achieve the therapeutic effect, for example, because such result has been established to a designated degree of statistical confidence, e.g., through administration to a relevant population.

[0048] ***Antibody***: As used herein, the term "antibody" refers to a polypeptide that includes canonical immunoglobulin sequence elements sufficient to confer specific binding to a particular target antigen. As is known in the art, intact antibodies as produced in nature are approximately 150 kD tetrameric agents comprised of two identical heavy chain polypeptides (about 50 kD each) and two identical light chain polypeptides (about 25 kD each) that associate with each other into what is commonly referred to as a "Y-shaped" structure. Each heavy chain is comprised of at least four domains (each about 110 amino acids long)– an amino-terminal variable (VH) domain (located at the tips of the Y structure), followed by three constant domains: CH1, CH2, and the carboxy-terminal CH3 (located at the base of the Y's stem). A short region, known as the "switch", connects the heavy chain variable and constant regions. The "hinge" connects CH2 and CH3 domains to the rest of the antibody. Two disulfide bonds in this hinge region connect the two heavy chain polypeptides to one another in an intact antibody. Each light chain is comprised of two domains – an amino-terminal variable (VL) domain, followed by a carboxy-terminal constant (CL) domain, separated from one another by another "switch". Intact antibody tetramers are comprised of two heavy chain-light chain dimers in which the heavy and light

chains are linked to one another by a single disulfide bond; two other disulfide bonds connect the heavy chain hinge regions to one another, so that the dimers are connected to one another and the tetramer is formed. Naturally-produced antibodies are also glycosylated, typically on the CH2 domain. Each domain in a natural antibody has a structure characterized by an "immunoglobulin fold" formed from two beta sheets (e.g., 3-, 4-, or 5-stranded sheets) packed against each other in a compressed antiparallel beta barrel. Each variable domain contains three hypervariable loops known as "complement determining regions" (CDR1, CDR2, and CDR3) and four somewhat invariant "framework" regions (FR1, FR2, FR3, and FR4). When natural antibodies fold, the FR regions form the beta sheets that provide the structural framework for the domains, and the CDR loop regions from both the heavy and light chains are brought together in three-dimensional space so that they create a single hypervariable antigen binding site located at the tip of the Y structure. The Fc region of naturally-occurring antibodies binds to elements of the complement system, and also to receptors on effector cells, including for example effector cells that mediate cytotoxicity. As is known in the art, affinity and/or other binding attributes of Fc regions for Fc receptors can be modulated through glycosylation or other modification. In some embodiments, antibodies produced and/or utilized in accordance with the present invention include glycosylated Fc domains, including Fc domains with modified or engineered such glycosylation. For purposes of the present invention, in certain embodiments, any polypeptide or complex of polypeptides that includes sufficient immunoglobulin domain sequences as found in natural antibodies can be referred to and/or used as an "antibody", whether such polypeptide is naturally produced (e.g., generated by an organism reacting to an antigen), or produced by recombinant engineering, chemical synthesis, or other artificial system or methodology. In some embodiments, an antibody is polyclonal; in some embodiments, an antibody is monoclonal. In some embodiments, an antibody has constant region sequences that are characteristic of mouse, rabbit, primate, or human antibodies. In some embodiments, antibody sequence elements are humanized, primatized, chimeric, etc, as is known in the art. Moreover, the term "antibody" as used herein, can refer in appropriate embodiments (unless otherwise stated or clear from context) to any of the art-known or developed constructs or formats for utilizing antibody structural and functional features in alternative presentation. For example, in some embodiments, an antibody utilized in accordance with the present invention is in a format selected from, but not limited to, intact IgA, IgG, IgE or IgM antibodies; bi- or multi- specific antibodies (e.g.,

Zybodies®, etc); antibody fragments such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd' fragments, Fd fragments, and isolated CDRs or sets thereof; single chain Fvs; polypeptide-Fc fusions; single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof); cameloid antibodies; masked antibodies (e.g., Probodies®); Small Modular ImmunoPharmaceuticals ("SMIPs™"); single chain or Tandem diabodies (TandAb®); VHHs; Anticalins®; Nanobodies® minibodies; BiTE®s; ankyrin repeat proteins or DARPINs®; Avimers®; DARTs; TCR-like antibodies;, Adnectins®; Affilins®; Trans-bodies®; Affibodies®; TrimerX®; MicroProteins; Fynomers®, Centyrins®; and KALBITOR®s. In some embodiments, an antibody may lack a covalent modification (e.g., attachment of a glycan) that it would have if produced naturally. In some embodiments, an antibody may contain a covalent modification (e.g., attachment of a glycan, a payload [e.g., a detectable moiety, a therapeutic moiety, a catalytic moiety, etc], or other pendant group [e.g., poly-ethylene glycol, etc.].

[0049] ***Antibody agent*:** As used herein, the term "antibody agent" refers to an agent that specifically binds to a particular antigen. In some embodiments, the term encompasses any polypeptide or polypeptide complex that includes immunoglobulin structural elements sufficient to confer specific binding. Exemplary antibody agents include, but are not limited to monoclonal antibodies or polyclonal antibodies. In some embodiments, an antibody agent may include one or more constant region sequences that are characteristic of mouse, rabbit, primate, or human antibodies. In some embodiments, an antibody agent may include one or more sequence elements are humanized, primatized, chimeric, etc, as is known in the art. In many embodiments, the term "antibody agent" is used to refer to one or more of the art-known or developed constructs or formats for utilizing antibody structural and functional features in alternative presentation. For example, embodiments, an antibody agent utilized in accordance with the present invention is in a format selected from, but not limited to, intact IgA, IgG, IgE or IgM antibodies; bi- or multi- specific antibodies (e.g., Zybodies®, etc); antibody fragments such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd' fragments, Fd fragments, and isolated CDRs or sets thereof; single chain Fvs; polypeptide-Fc fusions; single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof); cameloid antibodies; masked antibodies (e.g., Probodies®); Small Modular ImmunoPharmaceuticals ("SMIPs™"); single chain or Tandem diabodies (TandAb®); VHHs; Anticalins®; Nanobodies® minibodies; BiTE®s; ankyrin repeat

proteins or DARPINs®; Avimers®; DARTs; TCR-like antibodies;, Adnectins®; Affilins®; Trans-bodies®; Affibodies®; TrimerX®; MicroProteins; Fynomers®, Centyrins®; and KALBITOR®s. In some embodiments, an antibody may lack a covalent modification (e.g., attachment of a glycan) that it would have if produced naturally. In some embodiments, an antibody may contain a covalent modification (e.g., attachment of a glycan, a payload [e.g., a detectable moiety, a therapeutic moiety, a catalytic moiety, etc], or other pendant group [e.g., poly-ethylene glycol, etc.]. In many embodiments, an antibody agent is or comprises a polypeptide whose amino acid sequence includes one or more structural elements recognized by those skilled in the art as a complementarity determining region (CDR); in some embodiments an antibody agent is or comprises a polypeptide whose amino acid sequence includes at least one CDR (e.g., at least one heavy chain CDR and/or at least one light chain CDR) that is substantially identical to one found in a reference antibody. In some embodiments an included CDR is substantially identical to a reference CDR in that it is either identical in sequence or contains between 1-5 amino acid substitutions as compared with the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that it shows at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that it shows at least 96%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that at least one amino acid within the included CDR is deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that 1-5 amino acids within the included CDR are deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical to the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that at least one amino acid within the included CDR is substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments an included CDR is substantially identical to a reference CDR in that 1-5 amino acids within the included CDR are deleted, added, or substituted as compared with the reference CDR but the included CDR has an amino acid sequence that is otherwise identical to the reference CDR. In some embodiments,

an antibody agent is or comprises a polypeptide whose amino acid sequence includes structural elements recognized by those skilled in the art as an immunoglobulin variable domain. In some embodiments, an antibody agent is a polypeptide protein having a binding domain which is homologous or largely homologous to an immunoglobulin-binding domain.

[0050] ***Antibody component*:** as used herein, refers to a polypeptide element (that may be a complete polypeptide, or a portion of a larger polypeptide, such as for example a fusion polypeptide as described herein) that represents a portion of an antibody or antibody agent. In some embodiments, an antibody component includes one or more immunoglobulin structural features. In some embodiments, an antibody component specifically binds to an antigen. Typically, an antibody component is a polypeptide whose amino acid sequence includes elements characteristic of an antibody-binding region (e.g., an antibody light chain variable region or one or more complementarity determining regions ("*CDRs*") thereof, or an antibody heavy chain or variable region or one more CDRs thereof, optionally in presence of one or more framework regions). In some embodiments, an antibody component is or comprises a full-length antibody. In some embodiments, the term "*antibody component*" encompasses any protein having a binding domain, which is homologous or largely homologous to an immunoglobulin-binding domain. In particular embodiments, an included "antibody component" encompasses polypeptides having a binding domain that shows at least 99% identity with an immunoglobulin binding domain. In some embodiments, an included "antibody component" is any polypeptide having a binding domain that shows at least 70%, 75%, 80%, 85%, 90%, 95% or 98% identity with an immunoglobulin binding domain, for example a reference immunoglobulin binding domain. An included "*antibody component*" may have an amino acid sequence identical to that of an antibody (or a portion thereof, e.g., an antigen-binding portion thereof) that is found in a natural source. An antibody component may be monospecific, bi-specific, or multi-specific. An antibody component may include structural elements characteristic of any immunoglobulin class, including any of the human classes: IgG, IgM, IgA, IgD, and IgE. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Such antibody embodiments may also be bispecific, dual specific, or multi-specific formats specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "*antigen-binding portion*" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the

V_H, V_L, C_H1 and C_L domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_H1 domains; (iv) a Fv fragment consisting of the V_H and V_L domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341 :544-546), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_H and V_L, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_H and V_L regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). In some embodiments, an "*antibody component*", as described herein, is or comprises such a single chain antibody. In some embodiments, an "antibody component" is or comprises a diabody. Diabodies are bivalent, bispecific antibodies in which V_H and V_L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al., (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., (1994) Structure 2(12):1121-1123). Such antibody binding portions are known in the art (Kontermann and Dubel eds., Antibody Engineering (2001) Springer-Verlag. New York. 790 pp. (ISBN 3-540-41354-5). In some embodiments, an antibody component is or comprises a single chain "*linear antibody*" comprising a pair of tandem Fv segments (V_H-C_H1-V_H-C_H1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata et al., (1995) Protein Eng. 8(10): 1057-1062; and U.S. Patent No. 5,641,870). In some embodiments, an antibody component may have structural elements characteristic of chimeric or humanized antibodies. In general, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some embodiments, an antibody component may have structural elements characteristic of a human antibody.

[0051] ***Antigen***: The term “antigen”, as used herein, refers to an agent that elicits an immune response; and/or (ii) an agent that binds to a T cell receptor (*e.g.,* when presented by

an MHC molecule) or to an antibody. In some embodiments, an antigen elicits a humoral response (e.g., including production of antigen-specific antibodies); in some embodiments, an elicits a cellular response (e.g., involving T-cells whose receptors specifically interact with the antigen). In some embodiments, and antigen binds to an antibody and may or may not induce a particular physiological response in an organism. In general, an antigen may be or include any chemical entity such as, for example, a small molecule, a nucleic acid, a polypeptide, a carbohydrate, a lipid, a polymer (in some embodiments other than a biologic polymer [e.g., other than a nucleic acid or amino acid polymer) etc. In some embodiments, an antigen is or comprises a polypeptide. In some embodiments, an antigen is or comprises a glycan. Those of ordinary skill in the art will appreciate that, in general, an antigen may be provided in isolated or pure form, or alternatively may be provided in crude form (e.g., together with other materials, for example in an extract such as a cellular extract or other relatively crude preparation of an antigen-containing source). In some embodiments, antigens utilized in accordance with the present invention are provided in a crude form. In some embodiments, an antigen is a recombinant antigen.

[0052] ***Antigen presenting cell***: The phrase "antigen presenting cell" or "APC," as used herein, has its art understood meaning referring to cells which process and present antigens to T-cells. Exemplary antigen cells include dendritic cells, macrophages and certain activated epithelial cells.

[0053] ***Approximately***: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0054] ***Associated with***: Two events or entities are "associated" with one another, as that term is used herein, if the presence, level and/or form of one is correlated with that of the other. For example, a particular entity (e.g., polypeptide, genetic signature, metabolite, etc.) is considered to be associated with a particular disease, disorder, or condition, if its presence, level and/or form correlates with incidence of and/or susceptibility to the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, two or

more entities are physically "associated" with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another. In some embodiments, two or more entities that are physically associated with one another are covalently linked to one another; in some embodiments, two or more entities that are physically associated with one another are not covalently linked to one another but are non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and combinations thereof.

[0055] ***Binding***: It will be understood that the term "binding", as used herein, typically refers to a non-covalent association between or among two or more entities. "Direct" binding involves physical contact between entities or moieties; indirect binding involves physical interaction by way of physical contact with one or more intermediate entities. Binding between two or more entities can typically be assessed in any of a variety of contexts – including where interacting entities or moieties are studied in isolation or in the context of more complex systems (e.g., while covalently or otherwise associated with a carrier entity and/or in a biological system or cell).

[0056] ***Biological Sample***: As used herein, the term "biological sample" typically refers to a sample obtained or derived from a biological source (e.g., a tissue or organism or cell culture) of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, *etc.* In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy),

surgery, collection of body fluid (*e.g.,* blood, lymph, feces *etc.*), *etc.* In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, *etc.*

[0057] ***Biomarker:*** The term "biomarker" is used herein, consistent with its use in the art, to refer to a to an entity whose presence, level, or form, correlates with a particular biological event or state of interest, so that it is considered to be a "marker" of that event or state. To give but a few examples, in some embodiments, a biomarker may be or comprises a marker for a particular disease state, or for likelihood that a particular disease, disorder or condition may develop. In some embodiments, a biomarker may be or comprise a marker for a particular disease or therapeutic outcome, or likelihood thereof. Thus, in some embodiments, a biomarker is predictive, in some embodiments, a biomarker is prognostic, in some embodiments, a biomarker is diagnostic, of the relevant biological event or state of interest. A biomarker may be an entity of any chemical class. For example, in some embodiments, a biomarker may be or comprise a nucleic acid, a polypeptide, a lipid, a carbohydrate, a small molecule, an inorganic agent (e.g., a metal or ion), or a combination thereof. In some embodiments, a biomarker is a cell surface marker. In some embodiments, a biomarker is a gene. In some embodiments, a biomarker is a gene associated with a particular cell type. In some embodiments, a biomarker is intracellular. In some embodiments, a biomarker is found outside of cells (e.g., is secreted or is otherwise generated or present outside of cells, e.g., in a body fluid such as blood, urine, tears, saliva, cerebrospinal fluid, etc.). In some embodiments, a biomarker is a particular form (*e.g.*, variant form (*e.g.*, presence of a particular allele or mutation), modified form (*e.g.*, epigenetic modification of a gene or gene associated sequence, phosphorylation or glycosylation of a protein, etc.), a particular one of known forms (*e.g.*, splicing forms, allelelic forms, etc.), etc.) of one or more genes or gene products.

[0058] ***Cancer:*** The terms "cancer", "malignancy", "neoplasm", "tumor", and "carcinoma", are used interchangeably herein to refer to cells that exhibit relatively

abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In general, cells of interest for detection or treatment in the present application include precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and non-metastatic cells. The teachings of the present disclosure may be relevant to any and all cancers. To give but a few, non-limiting examples, in some embodiments, teachings of the present disclosure are applied to one or more cancers such as, for example, hematopoietic cancers including leukemias, lymphomas (Hodgkins and non-Hodgkins), myelomas and myeloproliferative disorders; sarcomas, melanomas, adenomas, carcinomas of solid tissue, squamous cell carcinomas of the mouth, throat, larynx, and lung, liver cancer, genitourinary cancers such as prostate, cervical, bladder, uterine, and endometrial cancer and renal cell carcinomas, bone cancer, pancreatic cancer, skin cancer, cutaneous or intraocular melanoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, head and neck cancers, breast cancer, gastro-intestinal cancers and nervous system cancers, benign lesions such as papillomas, and the like.

[0059] ***Cellular lysate***: As used herein, the term "cellular lysate" or "cell lysate" refers to a fluid containing contents of one or more disrupted cells (i.e., cells whose membrane has been disrupted). In some embodiments, a cellular lysate includes both hydrophilic and hydrophobic cellular components. In some embodiments, a cellular lysate includes predominantly hydrophilic components; in some embodiments, a cellular lysate includes predominantly hydrophobic components. In some embodiments, a cellular lysate is a lysate of one or more cells selected from the group consisting of plant cells, microbial (e.g., bacterial or fungal) cells, animal cells (e.g., mammalian cells), human cells, and combinations thereof. In some embodiments, a cellular lysate is a lysate of one or more abnormal cells, such as cancer cells. In some embodiments, a cellular lysate is a crude lysate in that little or no purification is performed after disruption of the cells; in some embodiments, such a lysate is referred to as a "primary" lysate. In some embodiments, one or more isolation or purification steps is performed on a primary lysate; however, the term "lysate" refers to a preparation that includes multiple cellular components and not to pure preparations of any individual component.

[0060] ***Characteristic sequence***: A "characteristic sequence" is a sequence that is found in all members of a family of polypeptides or nucleic acids, and therefore can be used by those of ordinary skill in the art to define members of the family.

[0061] ***Characteristic sequence element***: As used herein, the phrase "characteristic sequence element" refers to a sequence element found in a polymer (e.g., in a polypeptide or nucleic acid) that represents a characteristic portion of that polymer. In some embodiments, presence of a characteristic sequence element correlates with presence or level of a particular activity or property of the polymer. In some embodiments, presence (or absence) of a characteristic sequence element defines a particular polymer as a member (or not a member) of a particular family or group of such polymers. A characteristic sequence element typically comprises at least two monomers (e.g., amino acids or nucleotides). In some embodiments, a characteristic sequence element includes at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, or more monomers (e.g., contiguously linked monomers). In some embodiments, a characteristic sequence element includes at least first and second stretches of contiguous monomers spaced apart by one or more spacer regions whose length may or may not vary across polymers that share the sequence element.

[0062] ***Combination Therapy:*** As used herein, the term "combination therapy" refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (e.g., two or more therapeutic agents). In some embodiments, the two or more regimens may be administered simultaneously; in some embodiments, such regimens may be administered sequentially (e.g., all "doses" of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, "administration" of combination therapy may involve administration of one or more agent(s) or modality(ies) to a subject receiving the other agent(s) or modality(ies) in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (e.g., as part of a single chemical complex or covalent entity).

[0063] ***Comparable:*** As used herein, the term "comparable" refers to two or more agents, entities, situations, sets of conditions, etc., that may not be identical to one another

but that are sufficiently similar to permit comparison there between so that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, etc to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

[0064] ***Composition:*** A "composition" or a "pharmaceutical composition" according to this invention refers to the combination of two or more agents as described herein for co-administration or administration as part of the same regimen. It is not required in all embodiments that the combination of agents result in physical admixture, that is, administration as separate co-agents each of the components of the composition is possible; however many patients or practitioners in the field may find it advantageous to prepare a composition that is an admixture of two or more of the ingredients in a pharmaceutically acceptable carrier, diluent, or excipient, making it possible to administer the component ingredients of the combination at the same time.

[0065] ***Comprising:*** A composition or method described herein as "comprising" one or more named elements or steps is open-ended, meaning that the named elements or steps are essential, but other elements or steps may be added within the scope of the composition or method. To avoid prolixity, it is also understood that any composition or method described as "comprising" (or which "comprises") one or more named elements or steps also describes the corresponding, more limited composition or method "consisting essentially of" (or which "consists essentially of") the same named elements or steps, meaning that the composition or method includes the named essential elements or steps and may also include additional elements or steps that do not materially affect the basic and novel characteristic(s) of the composition or method. It is also understood that any composition or method described herein as "comprising" or "consisting essentially of" one or more named elements

or steps also describes the corresponding, more limited, and closed-ended composition or method "consisting of" (or "consists of") the named elements or steps to the exclusion of any other unnamed element or step. In any composition or method disclosed herein, known or disclosed equivalents of any named essential element or step may be substituted for that element or step.

[0066] ***Determine:*** Certain methodologies described herein include a step of "determining". Those of ordinary skill in the art, reading the present specification, will appreciate that such "determining" can utilize or be accomplished through use of any of a variety of techniques available to those skilled in the art, including for example specific techniques explicitly referred to herein. In some embodiments, determining involves manipulation of a physical sample. In some embodiments, determining involves consideration and/or manipulation of data or information, for example utilizing a computer or other processing unit adapted to perform a relevant analysis. In some embodiments, determining involves receiving relevant information and/or materials from a source. In some embodiments, determining involves comparing one or more features of a sample or entity to a comparable reference.

[0067] ***Dosage Form:*** As used herein, the term "dosage form" refers to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Each unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or agent administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

[0068] ***Diagnostic information***: As used herein, "diagnostic information" or "information for use in diagnosis" is information that is useful in determining whether a patient has a disease, disorder or condition and/or in classifying a disease, disorder or condition into a phenotypic category or any category having significance with regard to prognosis of a disease, disorder or condition, or likely response to treatment (either treatment in general or any particular treatment) of a disease, disorder or condition.

Similarly, "diagnosis" refers to providing any type of diagnostic information, including, but not limited to, whether a subject is likely to have or develop a disease, disorder or condition, state, staging or characteristic of a disease, disorder or condition as manifested in the subject, information related to the nature or classification of a tumor, information related to prognosis and/or information useful in selecting an appropriate treatment. Selection of treatment may include the choice of a particular therapeutic agent or other treatment modality such as surgery, radiation, etc., a choice about whether to withhold or deliver therapy, a choice relating to dosing regimen (e.g., frequency or level of one or more doses of a particular therapeutic agent or combination of therapeutic agents), etc.

[0069] ***Domain:*** The term "domain" as used herein refers to a section or portion of an entity. In some embodiments, a "domain" is associated with a particular structural and/or functional feature of the entity so that, when the domain is physically separated from the rest of its parent entity, it substantially or entirely retains the particular structural and/or functional feature. Alternatively or additionally, a domain may be or include a portion of an entity that, when separated from that (parent) entity and linked with a different (recipient) entity, substantially retains and/or imparts on the recipient entity one or more structural and/or functional features that characterized it in the parent entity. In some embodiments, a domain is a section or portion of a molecule (e.g., a small molecule, carbohydrate, lipid, nucleic acid, or polypeptide). In some embodiments, a domain is a section of a polypeptide; in some such embodiments, a domain is characterized by a particular structural element (e.g., a particular amino acid sequence or sequence motif, α-helix character, β-sheet character, coiled-coil character, random coil character, etc.), and/or by a particular functional feature (e.g., binding activity, enzymatic activity, folding activity, signaling activity, etc.).

[0070] ***Dosing Regimen:*** As used herein, the term "dosing regimen" refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same

unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0071] ***Effector function***: as used herein refers a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include but are not limited to antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and complement-mediated cytotoxicity (CMC). In some embodiments, an effector function is one that operates after the binding of an antigen, one that operates independent of antigen binding, or both.

[0072] ***Effector cell:*** as used herein refers to a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. In some embodiments, effector cells may include, but may not be limited to, one or more of monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, T-lymphocytes, B-lymphocytes and may be from any organism including but not limited to humans, mice, rats, rabbits, and monkeys.

[0073] ***Engineered***: Those of ordinary skill in the art, reading the present disclosure, will appreciate that the term "engineered", as used herein, refers to an aspect of having been manipulated and altered by the hand of man. In particular, the term "engineered cell" refers to a cell that has been subjected to a manipulation, so that its genetic, epigenetic, and/or phenotypic identity is altered relative to an appropriate reference cell such as otherwise identical cell that has not been so manipulated. In some embodiments, the manipulation is or comprises a genetic manipulation. In some embodiments, an engineered cell is one that has been manipulated so that it contains and/or expresses a particular agent of interest (e.g., a protein, a nucleic acid, and/or a particular form thereof) in an altered amount and/or according to altered timing relative to such an appropriate reference cell.

[0074] ***Epitope:*** as used herein, includes any moiety that is specifically recognized by an immunoglobulin (e.g., antibody or receptor) binding component. In some embodiments, an epitope is comprised of a plurality of chemical atoms or groups on an antigen. In some embodiments, such chemical atoms or groups are surface-exposed when the antigen adopts a relevant three-dimensional conformation. In some embodiments, such chemical atoms or groups are physically near to each other in space when the antigen adopts such a conformation. In some embodiments, at least some such chemical atoms are groups are physically separated from one another when the antigen adopts an alternative conformation (e.g., is linearized).

[0075] ***Excipient***: as used herein, refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example to provide or contribute to a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0076] ***Expression:*** As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5' cap formation, and/or 3' end formation); (3) translation of an RNA into a polypeptide or protein; and/or (4) post-translational modification of a polypeptide or protein.

[0077] ***Gene***: As used herein, the term "gene" refers to a DNA sequence in a chromosome that codes for a product (e.g., an RNA product and/or a polypeptide product). In some embodiments, a gene includes coding sequence (i.e., sequence that encodes a particular product); in some embodiments, a gene includes non-coding sequence. In some particular embodiments, a gene may include both coding (e.g., exonic) and non-coding (e.g., intronic) sequences. In some embodiments, a gene may include one or more regulatory elements that, for example, may control or impact one or more aspects of gene expression (e.g., cell-type-specific expression, inducible expression, etc.).

[0078] ***Gene product or expression product***: As used herein, the term "gene product" or "expression product" generally refers to an RNA transcribed from the gene (pre- and/or post-processing) or a polypeptide (pre- and/or post-modification) encoded by an RNA transcribed from the gene.

[0079] ***Genome***: As used herein, the term "genome" refers to the total genetic information carried by an individual organism or cell, represented by the complete DNA sequences of its chromosomes.

[0080] ***Genome Profile***: As used herein, the term "genome profile" refers to a representative subset of the total information contained within a genome. Typicaly, a genome profile contains genotypes at a particular set of polymorphic loci. In some embodiments, a genome profile may correlate with a particular feature, trait, or set thereof characteristic of, for example, a particular animal, line, breed, or crossbreed population.

[0081] ***Host***: The term "host" is used herein to refer to a system (e.g., a cell, organism, etc) in which a polypeptide of interest is present. In some embodiments, a host is a system that is susceptible to infection with a particular infectious agent. In some embodiments, a host is a system that expresses a particular polypeptide of interest.

[0082] ***Host cell***: as used herein, refers to a cell into which exogenous DNA (recombinant or otherwise) has been introduced. Persons of skill upon reading this disclosure will understand that such terms refer not only to the particular subject cell, but also to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "*host cell*" as used herein. In some embodiments, host cells include prokaryotic and eukaryotic cells selected from any of the Kingdoms of life that are suitable for expressing an exogenous DNA (e.g., a recombinant nucleic acid sequence). Exemplary cells include those of prokaryotes and eukaryotes (single-cell or multiple-cell), bacterial cells (e.g., strains of *E. coli, Bacillus spp., Streptomyces spp.*, etc.), mycobacteria cells, fungal cells, yeast cells (e.g., *S. cerevisiae, S. pombe, P. pastoris, P. methanolica*, etc.), plant cells, insect cells (e.g., SF-9, SF-21, baculovirus-infected insect cells, Trichoplusia ni, etc.), non-human animal cells, human cells, or cell fusions such as, for example, hybridomas or quadromas. In some embodiments, the cell is a human, monkey, ape, hamster, rat, or mouse cell. In some embodiments, the cell is eukaryotic and is selected from the following cells: CHO (e.g., CHO Kl, DXB-1 1 CHO, Veggie-CHO), COS (e.g., COS-7), retinal cell, Vero, CV1, kidney (e.g., HEK293, 293 EBNA, MSR 293, MDCK, HaK, BHK), HeLa, HepG2, WI38, MRC 5, Colo205, HB 8065, HL-60, (e.g., BHK21), Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT 060562, Sertoli cell, BRL 3 A cell, HT1080 cell,

myeloma cell, tumor cell, and a cell line derived from an aforementioned cell. In some embodiments, the cell comprises one or more viral genes.

[0083] ***"Improve," "increase", "inhibit"*** or ***"reduce"***: As used herein, the terms "improve", "increase", "inhibit', "reduce", or grammatical equivalents thereof, indicate values that are relative to a baseline or other reference measurement. In some embodiments, an appropriate reference measurement may be or comprise a measurement in a particular system (e.g., in a single individual) under otherwise comparable conditions absent presence of (e.g., prior to and/or after) a particular agent or treatment, or in presence of an appropriate comparable reference agent. In some embodiments, an appropriate reference measurement may be or comprise a measurement in comparable system known or expected to respond in a particular way, in presence of the relevant agent or treatment.

[0084] ***Inducible Effector Cell Surface Marker***: As used herein, the term "inducible effector cell surface marker" refers to an entity, that typically is or includes at least one polypeptide, expressed on the surface of immune effector cells, including without limitation natural killer (NK) cells, which expression is induced or significantly upregulated during activation of the effector cells. In some embodiments, increased surface expression involves increased localization of the marker on the cell surface (e.g., relative to in the cytoplasm or in secreted form, etc). Alternatively or additionally, in some embodiments, increased surface expression involves increased production of the marker by the cell. In some embodiments, increased surface expression of a particular inducible effector cell surface marker correlates with and/or participates in increased activity by the effector cell (e.g., increased antibody-mediated cellular cytotoxicity [ADCC]). In some embodiments, an inducible effector cell surface marker is selected from a group consisting of a member of the TNFR family, a member of the CD28 family, a cell adhesion molecule, a vascular adhesion molecule, a G protein regulator, an immune cell activating protein, a recruiting chemokine/cytokine, a receptor for a recruiting chemokine/cytokine, an ectoenzyme, a member of the immunoglobulin superfamily, a lysosomal associated membrane protein. Certain exemplary inducible cell surface markers include, without limitation, CD38, CD137, OX40, GITR, CD30, ICOS, etc. In some particular embodiments, the term refers to any of the above-mentioned inducible cell surface markers other than CD38.

[0085] ***Inhibitory agent:*** As used herein, the term "inhibitory agent" refers to an entity, condition, or event whose presence, level, or degree correlates with decreased level or

activity of a target). In some embodiments, an inhibitory agent may be act directly (in which case it exerts its influence directly upon its target, for example by binding to the target); in some embodiments, an inhibitory agent may act indirectly (in which case it exerts its influence by interacting with and/or otherwise altering a regulator of the target, so that level and/or activity of the target is reduced). In some embodiments, an inhibitory agent is one whose presence or level correlates with a target level or activity that is reduced relative to a particular reference level or activity (e.g., that observed under appropriate reference conditions, such as presence of a known inhibitory agent, or absence of the inhibitory agent in question, etc.).

[0086] ***In vitro*:** The term "in vitro" as used herein refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, etc., rather than within a multi-cellular organism.

[0087] ***In vivo:*** as used herein refers to events that occur within a multi-cellular organism, such as a human and a non-human animal. In the context of cell-based systems, the term may be used to refer to events that occur within a living cell (as opposed to, for example, *in vitro* systems).

[0088] ***Isolated:*** as used herein, refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) designed, produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% of the other components with which they were initially associated. In some embodiments, isolated agents are about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "*pure*" if it is substantially free of other components. In some embodiments, as will be understood by those skilled in the art, a substance may still be considered "*isolated*" or even "*pure*", after having been combined with certain other components such as, for example, one or more carriers or excipients (e.g., buffer, solvent, water, etc.); in such embodiments, percent isolation or purity of the substance is calculated without including such carriers or excipients. To give but one

example, in some embodiments, a biological polymer such as a polypeptide or polynucleotide that occurs in nature is considered to be "*isolated*" when, a) by virtue of its origin or source of derivation is not associated with some or all of the components that accompany it in its native state in nature; b) it is substantially free of other polypeptides or nucleic acids of the same species from the species that produces it in nature; c) is expressed by or is otherwise in association with components from a cell or other expression system that is not of the species that produces it in nature. Thus, for instance, in some embodiments, a polypeptide that is chemically synthesized or is synthesized in a cellular system different from that which produces it in nature is considered to be an "*isolated*" polypeptide. Alternatively or additionally, in some embodiments, a polypeptide that has been subjected to one or more purification techniques may be considered to be an "*isolated*" polypeptide to the extent that it has been separated from other components a) with which it is associated in nature; and/or b) with which it was associated when initially produced.

[0089] ***Marker:*** A marker, as used herein, refers to an entity or moiety whose presence or level is a characteristic of a particular state or event. In some embodiments, presence or level of a particular marker may be characteristic of presence or stage of a disease, disorder, or condition. To give but one example, in some embodiments, the term refers to a gene expression product that is characteristic of a particular tumor, tumor subclass, stage of tumor, etc. Alternatively or additionally, in some embodiments, a presence or level of a particular marker correlates with activity (or activity level) of a particular signaling pathway, for example that may be characteristic of a particular class of tumors. The statistical significance of the presence or absence of a marker may vary depending upon the particular marker. In some embodiments, detection of a marker is highly specific in that it reflects a high probability that the tumor is of a particular subclass. Such specificity may come at the cost of sensitivity (i.e., a negative result may occur even if the tumor is a tumor that would be expected to express the marker). Conversely, markers with a high degree of sensitivity may be less specific that those with lower sensitivity. According to the present invention a useful marker need not distinguish tumors of a particular subclass with 100% accuracy.

[0090] ***Nucleic acid***: As used herein, in its broadest sense, refers to any compound and/or substance that is or can be incorporated into an oligonucleotide chain. In some embodiments, a nucleic acid is a compound and/or substance that is or can be incorporated

into an oligonucleotide chain via a phosphodiester linkage. As will be clear from context, in some embodiments, "*nucleic acid*" refers to an individual nucleic acid residue (e.g., a nucleotide and/or nucleoside); in some embodiments, "*nucleic acid*" refers to an oligonucleotide chain comprising individual nucleic acid residues. In some embodiments, a "*nucleic acid*" is or comprises RNA; in some embodiments, a "*nucleic acid*" is or comprises DNA. In some embodiments, a nucleic acid is, comprises, or consists of one or more natural nucleic acid residues. In some embodiments, a nucleic acid is, comprises, or consists of one or more nucleic acid analogs. In some embodiments, a nucleic acid analog differs from a nucleic acid in that it does not utilize a phosphodiester backbone. For example, in some embodiments, a nucleic acid is, comprises, or consists of one or more "*peptide nucleic acids*", which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. Alternatively or additionally, in some embodiments, a nucleic acid has one or more phosphorothioate and/or 5'-N-phosphoramidite linkages rather than phosphodiester bonds. In some embodiments, a nucleic acid is, comprises, or consists of one or more natural nucleosides (e.g., adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxy guanosine, and deoxycytidine). In some embodiments, a nucleic acid is, comprises, or consists of one or more nucleoside analogs (e.g., 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3 -methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5 -propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, 0(6)-methylguanine, 2-thiocytidine, methylated bases, intercalated bases, and combinations thereof). In some embodiments, a nucleic acid comprises one or more modified sugars (e.g., 2'-fluororibose, ribose, 2'-deoxyribose, arabinose, and hexose) as compared with those in natural nucleic acids. In some embodiments, a nucleic acid has a nucleotide sequence that encodes a functional gene product such as an RNA or protein. In some embodiments, a nucleic acid includes one or more introns. In some embodiments, nucleic acids are prepared by one or more of isolation from a natural source, enzymatic synthesis by polymerization based on a complementary template (*in vivo* or *in vitro*), reproduction in a recombinant cell or system, and chemical synthesis. In some embodiments, a nucleic acid is at least 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 1 10, 120, 130, 140, 150, 160, 170, 180, 190, 20, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500,

600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 or more residues long. In some embodiments, a nucleic acid is partly or wholly single stranded; in some embodiments, a nucleic acid is partly or wholly double stranded. In some embodiments a nucleic acid has a nucleotide sequence comprising at least one element that encodes, or is the complement of a sequence that encodes, a polypeptide. In some embodiments, a nucleic acid has enzymatic activity.

[0091] ***Patient:*** As used herein, the term "patient" or "subject" refers to any organism to which a provided composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. A human includes pre and post natal forms. In some embodiments, a patient is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient displays one or more symptoms of a disorder or condition. In some embodiments, a patient has been diagnosed with one or more disorders or conditions

[0092] ***Pharmaceutically Acceptable:*** As used herein, the term "pharmaceutically acceptable" applied to the carrier, diluent, or excipient used to formulate a composition as disclosed herein means that the carrier, diluent, or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0093] ***Pharmaceutical Composition***: As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release

patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0094] ***Polypeptide***: As used herein refers to any polymeric chain of amino acids. In some embodiments, a polypeptide has an amino acid sequence that occurs in nature. In some embodiments, a polypeptide has an amino acid sequence that does not occur in nature. In some embodiments, a polypeptide has an amino acid sequence that is engineered in that it is designed and/or produced through action of the hand of man. In some embodiments, a polypeptide may comprise or consist of natural amino acids, non-natural amino acids, or both. In some embodiments, a polypeptide may comprise or consist of only natural amino acids or only non-natural amino acids. In some embodiments, a polypeptide may comprise D-amino acids, L-amino acids, or both. In some embodiments, a polypeptide may comprise only D-amino acids. In some embodiments, a polypeptide may comprise only L-amino acids. In some embodiments, a polypeptide may include one or more pendant groups or other modifications, e.g., modifying or attached to one or more amino acid side chains, at the polypeptide's N-terminus, at the polypeptide's C-terminus, or any combination thereof. In some embodiments, such pendant groups or modifications may be selected from the group consisting of acetylation, amidation, lipidation, methylation, pegylation, etc., including combinations thereof. In some embodiments, a polypeptide may be cyclic, and/or may comprise a cyclic portion. In some embodiments, a polypeptide is not cyclic and/or does not comprise any cyclic portion. In some embodiments, a polypeptide is linear. In some embodiments, a polypeptide may be or comprise a stapled polypeptide. In some embodiments, the term "polypeptide" may be appended to a name of a reference polypeptide, activity, or structure; in such instances it is used herein to refer to polypeptides that share the relevant activity or structure and thus can be considered to be members of the same class or family of polypeptides. For each such class, the present specification provides and/or those skilled in the art will be aware of exemplary polypeptides within the class whose amino acid sequences and/or functions are known; in some embodiments, such exemplary polypeptides are reference polypeptides for the polypeptide class or family. In some embodiments, a member of a polypeptide class or family shows significant sequence homology or identity with, shares a common sequence motif (e.g., a characteristic sequence element) with, and/or shares a common activity (in some embodiments at a comparable level

or within a designated range) with a reference polypeptide of the class; in some embodiments with all polypeptides within the class). For example, in some embodiments, a member polypeptide shows an overall degree of sequence homology or identity with a reference polypeptide that is at least about 30-40%, and is often greater than about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more and/or includes at least one region (e.g., a conserved region that may in some embodiments be or comprise a characteristic sequence element) that shows very high sequence identity, often greater than 90% or even 95%, 96%, 97%, 98%, or 99%. Such a conserved region usually encompasses at least 3-4 and often up to 20 or more amino acids; in some embodiments, a conserved region encompasses at least one stretch of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous amino acids. In some embodiments, a relevant polypeptide may comprise or consist of a fragment of a parent polypeptide. In some embodiments, a useful polypeptide as may comprise or consist of a plurality of fragments, each of which is found in the same parent polypeptide in a different spatial arrangement relative to one another than is found in the polypeptide of interest (e.g., fragments that are directly linked in the parent may be spatially separated in the polypeptide of interest or vice versa, and/or fragments may be present in a different order in the polypeptide of interest than in the parent), so that the polypeptide of interest is a derivative of its parent polypeptide.

[0095] ***Prevent or prevention***: as used herein when used in connection with the occurrence of a disease, disorder, and/or condition, refers to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. In some embodiments, prevention is assessed on a population basis such that an agent is considered to "prevent" a particular disease, disorder or condition if a statistically significant decrease in the development, frequency, and/or intensity of one or more symptoms of the disease, disorder or condition is observed in a population susceptible to the disease, disorder, or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0096] ***Prognostic and predictive information***: As used herein, the terms "prognostic information" and "predictive information" are used to refer to any information that may be used to indicate any aspect of the course of a disease or condition either in the absence or presence of treatment. Such information may include, but is not limited to, the

average life expectancy of a patient, the likelihood that a patient will survive for a given amount of time (e.g., 6 months, 1 year, 5 years, etc.), the likelihood that a patient will be cured of a disease, the likelihood that a patient's disease will respond to a particular therapy (wherein response may be defined in any of a variety of ways). Prognostic and predictive information are included within the broad category of diagnostic information.

[0097] ***Protein***: As used herein, the term "protein" refers to a polypeptide (*i.e.*, a string of at least two amino acids linked to one another by peptide bonds). Proteins may include moieties other than amino acids (*e.g.*, may be glycoproteins, proteoglycans, etc.) and/or may be otherwise processed or modified. Those of ordinary skill in the art will appreciate that a "protein" can be a complete polypeptide chain as produced by a cell (with or without a signal sequence), or can be a characteristic portion thereof. Those of ordinary skill will appreciate that a protein can sometimes include more than one polypeptide chain, for example linked by one or more disulfide bonds or associated by other means. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful modifications include, *e.g.*, terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0098] ***Receptor tyrosine kinase***: The term "receptor tyrosine kinase", as used herein, refers to any members of the protein family of receptor tyrosine kinases (RTK), which includes but is not limited to sub-families such as Epidermal Growth Factor Receptors (EGFR) (including ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4), Fibroblast Growth Factor Receptors (FGFR) (including FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF18, and FGF21) Vascular Endothelial Growth Factor Receptors (VEGFR) (including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PIGF), RET Receptor and the Eph Receptor Family (including EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphA9, EphA10, EphB1, EphB2. EphB3, EphB4, and EphB6).

[0099] ***Reference***: As used herein describes a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence or value of interest is compared with a reference or control agent, animal, individual, population, sample, sequence or value. In some embodiments, a reference or control is tested and/or determined substantially simultaneously with the testing or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Typically, as would be understood by those skilled in the art, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. Those skilled in the art will appreciate when sufficient similarities are present to justify reliance on and/or comparison to a particular possible reference or control.

[0100] ***Refractory:*** The term "refractory" as used herein, refers to any subject or condition that does not respond with an expected clinical efficacy following the administration of provided compositions as normally observed by practicing medical personnel.

[0101] ***Response:*** As used herein, a response to treatment may refer to any beneficial alteration in a subject's condition that occurs as a result of or correlates with treatment. Such alteration may include stabilization of the condition (e.g., prevention of deterioration that would have taken place in the absence of the treatment), amelioration of symptoms of the condition, and/or improvement in the prospects for cure of the condition, etc. It may refer to a subject's response or to a tumor's response. Tumor or subject response may be measured according to a wide variety of criteria, including clinical criteria and objective criteria. Techniques for assessing response include, but are not limited to, clinical examination, positron emission tomography, chest X-ray CT scan, MRI, ultrasound, endoscopy, laparoscopy, presence or level of tumor markers in a sample obtained from a subject, cytology, and/or histology. Many of these techniques attempt to determine the size of a tumor or otherwise determine the total tumor burden. Methods and guidelines for assessing response to treatment are discussed in Therasse et. al., "New guidelines to evaluate the response to treatment in solid tumors", European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada, *J. Natl. Cancer Inst.*, 2000, 92(3):205-216. The exact response criteria can be selected in any appropriate manner, provided that when comparing groups of tumors

and/or patients, the groups to be compared are assessed based on the same or comparable criteria for determining response rate. One of ordinary skill in the art will be able to select appropriate criteria.

[0102] ***Sample:*** As used herein, the term "sample" typically refers to a biological sample obtained or derived from a source of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, *etc.* In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy), surgery, collection of body fluid (*e.g.*, blood, lymph, feces *etc.*), *etc.* In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, *etc.*

[0103] ***Solid Tumor:*** As used herein, the term "solid tumor" refers to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign or malignant. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, lymphomas, mesothelioma, neuroblastoma, retinoblastoma, etc.

[0104] ***Specific***: The term "specific", when used herein with reference to an agent having an activity, is understood by those skilled in the art to mean that the agent discriminates between potential target entities or states. For example, an in some embodiments, an agent is said to bind "specifically" to its target if it binds preferentially with that target in the presence of one or more competing alternative targets. In many embodiments, specific interaction is dependent upon the presence of a particular structural feature of the target entity (e.g., an epitope, a cleft, a binding site). It is to be understood that specificity need not be absolute. In some embodiments, specificity may be evaluated relative to that of the binding agent for one or more other potential target entities (e.g., competitors). In some embodiments, specificity is evaluated relative to that of a reference specific binding agent. In some embodiments specificity is evaluated relative to that of a reference non-specific binding agent. In some embodiments, the agent or entity does not detectably bind to the competing alternative target under conditions of binding to its target entity. In some embodiments, binding agent binds with higher on-rate, lower off-rate, increased affinity, decreased dissociation, and/or increased stability to its target entity as compared with the competing alternative target(s).

[0105] ***Stage of cancer:*** As used herein, the term "stage of cancer" refers to a qualitative or quantitative assessment of the level of advancement of a cancer. In some embodiments, criteria used to determine the stage of a cancer may include, but are not limited to, one or more of where the cancer is located in a body, tumor size, whether the cancer has spread to lymph nodes, whether the cancer has spread to one or more different parts of the body, etc. In some embodiments, cancer may be staged using the so-called TNM System, according to which T refers to the size and extent of the main tumor, usually called the primary tumor; N refers to the the number of nearby lymph nodes that have cancer; and M refers to whether the cancer has metastasized. In some embodiments, a cancer may be referred to as Stage 0 (abnormal cells are present but have not spread to nearby tissue, also called carcinoma *in situ*, or CIS; CIS is not cancer, but it may become cancer), Stage I-III (cancer is present; the higher the number, the larger the tumor and the more it has spread into nearby tissues), or Stage IV (the cancer has spread to distant parts of the body). In some embodiments, a cancer may be assigned to a stage selected from the group consisting of: *in situ* (abnormal cells are present but have not spread to nearby tissue); localized (cancer is limited to the place where it started, with no sign that it has spread);

regional (cancer has spread to nearby lymph nodes, tissues, or organs): distant (cancer has spread to distant parts of the body); and unknown (there is not enough information to figure out the stage).

[0106] ***Subject***: As used herein, the term "subject" or "test subject" refers to any organism to which a provided compound or composition is administered in accordance with the present disclosure *e.g.,* for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.,* mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; *etc.*) and plants. In some embodiments, a subject may be suffering from, and/or susceptible to a disease, disorder, and/or condition. In some embodiments, terms "*individual*" or "*patient*" are used and are intended to be interchangeable with "*subject*". In some embodiments, a subject is suffering from a relevant disease, disorder or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms or characteristics of a disease, disorder or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0107] ***Suffering from***: An individual who is "suffering from" a disease, disorder, and/or condition displays one or more symptoms of a disease, disorder, and/or condition and/or has been diagnosed with the disease, disorder, or condition.

[0108] ***Substantially:*** As used herein, the term "*substantially*" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "*substantially*" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0109] ***Surrogate Marker***: The term "surrogate marker", as used herein, refers to an entity whose presence, level, or form, may act as a proxy for presence, level, or form of another entity (e.g., a biomarker) of interest. Typically, a surrogate marker may be easier to

detect or analyze (e.g., quantify) than is the entity of interest. To give but one example, in some embodiments, where the entity of interest is a protein, an expressed nucleic acid (e.g., mRNA) encoding the protein may sometimes be utilized as a surrogate marker for the protein (or its level). To give another example, in some embodiments, where the entity of interest is an enzyme, a product of the enzyme's activity may sometimes be utilized as a surrogate marker for the enzyme (or its activity level). To give one more example, in some embodiments, where the entity of interest is a small molecule, a metabolite of the small molecule may sometimes be used as a surrogate marker for the small molecule.

[0110] ***Susceptible to***: An individual who is "susceptible to" a disease, disorder, or condition is at risk for developing the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition does not display any symptoms of the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition has not been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition is an individual who has been exposed to conditions associated with development of the disease, disorder, or condition. In some embodiments, a risk of developing a disease, disorder, and/or condition is a population-based risk (e.g., family members of individuals suffering from the disease, disorder, or condition).

[0111] ***Symptoms are reduced***: According to the present invention, "symptoms are reduced" when one or more symptoms of a particular disease, disorder or condition is reduced in magnitude (e.g., intensity, severity, etc.) and/or frequency. For purposes of clarity, a delay in the onset of a particular symptom is considered one form of reducing the frequency of that symptom.

[0112] ***Systemic***: The phrases "systemic administration," "administered systemically," "peripheral administration," and "administered peripherally" as used herein have their art-understood meaning referring to administration of a compound or composition such that it enters the recipient's system.

[0113] ***Therapeutic agent***: As used herein, the phrase "therapeutic agent" in general refers to any agent that elicits a desired pharmacological effect when administered to an organism. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, the appropriate population may be a population of model organisms. In some

embodiments, an appropriate population may be defined by various criteria, such as a certain age group, gender, genetic background, preexisting clinical conditions, etc. In some embodiments, a therapeutic agent is a substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans.

[0114] ***Therapeutic Regimen:*** A "therapeutic regimen", as that term is used herein, refers to a dosing regimen whose administration across a relevant population is correlated with a desired or beneficial therapeutic outcome.

[0115] ***Therapeutically Effective Amount:*** As used herein, the term "therapeutically effective amount" means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, stabilizes one or more characteristics of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term "therapeutically effective amount" does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. For example, in some embodiments, term "therapeutically effective amount", refers to an amount which, when administered to an individual in need thereof in the context of inventive therapy, will block, stabilize, attenuate, or reverse a cancer-supportive process occurring in said individual, or will enhance or increase a cancer-suppressive process in said individual. In the context of cancer treatment, a "therapeutically effective amount" is an amount which, when administered to an individual diagnosed with a cancer, will prevent, stabilize, inhibit, or reduce the further development of cancer in the individual. A particularly preferred "therapeutically effective amount" of a composition described herein reverses (in a therapeutic treatment) the development of a malignancy such as a pancreatic

carcinoma or helps achieve or prolong remission of a malignancy. A therapeutically effective amount administered to an individual to treat a cancer in that individual may be the same or different from a therapeutically effective amount administered to promote remission or inhibit metastasis. As with most cancer therapies, the therapeutic methods described herein are not to be interpreted as, restricted to, or otherwise limited to a "cure" for cancer; rather the methods of treatment are directed to the use of the described compositions to "treat" a cancer, i.e., to effect a desirable or beneficial change in the health of an individual who has cancer. Such benefits are recognized by skilled healthcare providers in the field of oncology and include, but are not limited to, a stabilization of patient condition, a decrease in tumor size (tumor regression), an improvement in vital functions (e.g., improved function of cancerous tissues or organs), a decrease or inhibition of further metastasis, a decrease in opportunistic infections, an increased survivability, a decrease in pain, improved motor function, improved cognitive function, improved feeling of energy (vitality, decreased malaise), improved feeling of well-being, restoration of normal appetite, restoration of healthy weight gain, and combinations thereof. In addition, regression of a particular tumor in an individual (e.g., as the result of treatments described herein) may also be assessed by taking samples of cancer cells from the site of a tumor such as a pancreatic adenocarcinoma (e.g., over the course of treatment) and testing the cancer cells for the level of metabolic and signaling markers to monitor the status of the cancer cells to verify at the molecular level the regression of the cancer cells to a less malignant phenotype. For example, tumor regression induced by employing the methods of this invention would be indicated by finding a decrease in any of the pro-angiogenic markers discussed above, an increase in anti-angiogenic markers described herein, the normalization (i.e., alteration toward a state found in normal individuals not suffering from cancer) of metabolic pathways, intercellular signaling pathways, or intracellular signaling pathways that exhibit abnormal activity in individuals diagnosed with cancer. Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount may be formulated and/or administered in a single dose. In some embodiments, a therapeutically effective amount may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen.

[0116] ***Treatment***: As used herein, the term “treatment” (also “treat” or “treating”) refers to administration of a therapy that partially or completely alleviates, ameliorates,

relives, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition. Thus, in some embodiments, treatment may be prophylactic; in some embodiments, treatment may be therapeutic.

[0117] ***Tumor***: As used herein, the term "tumor" refers to an abnormal growth of cells or tissue. In some embodiments, a tumor may comprise cells that are precancerous (*e.g.*, benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. In some embodiments, a tumor is associated with, or is a manifestation of, a cancer. In some embodiments, a tumor may be a disperse tumor or a liquid tumor. In some embodiments, a tumor may be a solid tumor.

[0118]

[0119] ***Variant:*** As used herein, the term "variant" refers to an entity that shows significant structural identity with a reference entity but differs structurally from the reference entity in the presence or level of one or more chemical moieties as compared with the reference entity. In many embodiments, a variant also differs functionally from its reference entity. In general, whether a particular entity is properly considered to be a "variant" of a reference entity is based on its degree of structural identity with the reference entity. As will be appreciated by those skilled in the art, any biological or chemical reference entity has certain characteristic structural elements. A variant, by definition, is a distinct chemical entity that shares one or more such characteristic structural elements. To give but a few examples, a small molecule may have a characteristic core structural element (e.g., a macrocycle core) and/or one or more characteristic pendent moieties so that a variant of the small molecule is one that shares the core structural element and the characteristic pendent moieties but differs in other pendent moieties and/or in types of bonds present

(single vs double, E vs Z, etc.) within the core, a polypeptide may have a characteristic sequence element comprised of a plurality of amino acids having designated positions relative to one another in linear or three-dimensional space and/or contributing to a particular biological function, a nucleic acid may have a characteristic sequence element comprised of a plurality of nucleotide residues having designated positions relative to on another in linear or three-dimensional space. For example, a variant polypeptide may differ from a reference polypeptide as a result of one or more differences in amino acid sequence and/or one or more differences in chemical moieties (e.g., carbohydrates, lipids, etc.) covalently attached to the polypeptide backbone. In some embodiments, a variant polypeptide shows an overall sequence identity with a reference polypeptide that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, or 99%. Alternatively or additionally, in some embodiments, a variant polypeptide does not share at least one characteristic sequence element with a reference polypeptide. In some embodiments, the reference polypeptide has one or more biological activities. In some embodiments, a variant polypeptide shares one or more of the biological activities of the reference polypeptide. In some embodiments, a variant polypeptide lacks one or more of the biological activities of the reference polypeptide. In some embodiments, a variant polypeptide shows a reduced level of one or more biological activities as compared with the reference polypeptide. In many embodiments, a polypeptide of interest is considered to be a "variant" of a parent or reference polypeptide if the polypeptide of interest has an amino acid sequence that is identical to that of the parent but for a small number of sequence alterations at particular positions. Typically, fewer than 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% of the residues in the variant are substituted as compared with the parent. In some embodiments, a variant has 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 substituted residue as compared with a parent. Often, a variant has a very small number (e.g., fewer than 5, 4, 3, 2, or 1) number of substituted functional residues (i.e., residues that participate in a particular biological activity). Furthermore, a variant typically has not more than 5, 4, 3, 2, or 1 additions or deletions, and often has no additions or deletions, as compared with the parent. Moreover, any additions or deletions are typically fewer than about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 10, about 9, about 8, about 7, about 6, and commonly are fewer than about 5, about 4, about 3, or about 2 residues. In some embodiments, the parent or reference polypeptide is one found in nature. As will be understood by those of ordinary skill in the art, a plurality of variants of a

particular polypeptide of interest may commonly be found in nature, particularly when the polypeptide of interest is an infectious agent polypeptide.

Detailed Description of Certain Embodiments

Cancer Subtype Classification

[0120] Molecular classification of cancer subtypes is becoming an increasingly important tool, both for understanding tumor development and progression, and for designing treatment plans for particular tumors and/or tumor subtypes. Indeed, potential new therapies are now commonly evaluated and/or approved based on presence of a particular molecular signature established to correlate with responsiveness to the relevant therapy (and/or absence of a molecular signature established to negatively correlate with such responsiveness), for example as may be assessed via basket trials, and/or based on molecular subtyping of a relevant disease, disorder or condition, for example as may be assessed via umbrella trials. *See,* for example, Park *et al.* "An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians" *CA Cancer J Clin* 70:125, March/April 2020, incorporated herein by reference in its entirety.

[0121] Work by Lehmann *et al.* (*See* Lehman *et al.* "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies" *J Clin Invest*, 121(7), 2011, incorporated herein by reference in its entirety) has demonstrated that triple negative breast cancer (TNBC) tumors can be classified into subtypes through analysis of gene expression signatures. Lehmann *et al.* determined gene expression profiles for annotated genes within publicly available TNBC samples and performed centroid-based cluster analysis based upon the 20% of genes with the highest and lowest expression levels in at least 50% of the samples (2188 genes total). Clusters were categorized based upon features of differentially expressed genes, leading to identification of six different subtypes, specifically: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like MSL), and luminal androgen receptor (LAR). It was found that there was significant heterogeneity within TNBC tumors. Furthermore, Lehmann *et al* reported that certain cell lines representative of different subtypes showed differential response to certain therapies. Table 1 below summarizes the specific findings reported in Lehmann *et al.*:

[0122] Table 1: Tumor subtypes from Lehman *et al.*

Tumor Subtype	Highly Expressed Genes	Treatments to which Representative Cell Lines Respond
BL1 and BL2	Cell cycle genes DNA repair genes	Cisplatin
IM	Genes involved in immune cell processes	NA
M and MSL	Genes involved in epithelial-mesenchymal transition Growth factor pathway genes	NVP-BEX235 (a PI3K/mTOR inhibitor) Dasantinib (an abl/src inhibitor)
LAR	Androgen receptor signaling genes	Bicalutimide (an AR antagonist)

[0123] Lehmann et al. concluded that gene expression analyses can be useful to define distinct subtypes of TNBC, and further proposed that such analyses "may provide biomarkers that can be used for patient selection in the design of clinical trials for TNBC and/or as potential markers for response to treatment"; Lehmann et al also recommended that further such analyses, together with RNAi loss-of-function screens be performed in order to "identify new components of the "driver" signaling pathways in each of these subtypes that can be targeted in future drug discovery efforts for TNBC". See last paragraph of "Conclusion" section of, Lehman et al. "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies" J Clin Invest, 121(7), 2011.

[0124] Ring *et al.* (*See*, Ring *et al.* "Generation of an algorithm based on minimal gene sets to clinically subtype triple negative breast cancer patients" *BMC Cancer*, 16, February 2016, incorporated herein by reference in its entirety) independently analyzed the same gene expression datasets utilized by Lehman *et al.*, to identify genes enriched in different TNBC subtypes, and then further performed shrunken centroid analysis and elastic-net regularized linear modeling to define a set of genes whose expression could be analyzed to classify TNBC samples into the defined subtypes. Specifically, Ring *et al.* used linear regression, targeted maximum likelihood estimation, random forest, and elastic-net regularized linear models to create subclassifying models, with each subclass (subtype) being defined by an individual model (*See*, Subramanian *et al.*, "Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles",

PNAS, 102, 2015; *see also*, Friedman *et al.*, "Regularization Paths for Generalized Linear Models via Coordinate Descent", *J Stat Softw*, 33, 2010; *see also*, Hajian-Tilaki *et al.*, "Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation", 4, 2013, each of which is incorporated herein by reference in its entirety). Genes found to contribute to the individual subtype models were combined to create a 101-gene centroid model for TNBC subtype classification. This Ring *et al.* model represented a significant simplification, relative to the Lehmann *et al.* model, which relied on expression information for 2188 genes.

[0125] Furthermore, Ring *et al.* observed that gene expression Lehmann *et al.* had associated with the IM tumor subtype in fact was not reflective of tumor-cell expression at all but likely reflected presence of tumor infiltrating lymphocytes (TIL) in relevant tumor samples. Exclusion of IM gene signatures led to loss of information for samples, so the IM subtype was removed and cases initially assigned to this classification were analyzed separately. As a result, Ring *et al.* reduced the TNBC classes to five subtypes: BL1, BL2, LAR, M, and MSL; each of which could be reliably identified through use of the reduced 101-gene panel.

[0126] Ring *et al.* also reported preliminary evidence that subtype classification using its 101 gene model could be useful for predicting patient outcomes for certain therapies. For example, Ring *et al* reported that BL1 and BL2 TNBC subtypes, as defined using its 101 gene model, differ in their pathological response to mitotic inhibitors; BL1 subtype tumors tended to have a better response rate. As other classification approaches (including both the Lehmann *et al.* 2188-gene model and traditional pathological assessments) had similarly noted better prognosis for chemotherapy with BL1 subtype tumors relative to BL2 subtype, this finding was considered to provide initial validation that the Ring *et al.* 101 gene model represented important progress toward development of predictive assessment tool; however Ring *et al* itself notes both that further clinical validation of predictive success would be required to establish a medically useful tool and, furthermore, that reduced gene sets able "to individually classify each subtype" still needed to be developed.

[0127] It is worth noting that, in subsequent work, Lehmann *et al.* observed that tumors assigned by the 2188 gene model to a primary M classification did not have a secondary correlation to the IM subtype also defined by that model. *See*, Lehmann *et al.*

"Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection ", 11, June 2016, incorporated herein by reference. In fact, M subtype tumors demonstrated a strong negative correlation with the gene expression features of the IM subtype. As noted above, Ring *et al* subsequently established that the IM signature observed by Lehmann *et al* was not in fact a tumor subtype, but rather represented presence of TIL in the samples. This observation that the IM signature represented gene expression by TIL was confirmed by Grigoriadis *et al.,* who furthermore noted that each of the five actual tumor subtypes could be further classified by either a positive or negative IM gene signature. *See,* Grigoriadis *et al.* "Mesenchymal subtype negatively associates with the presence of immune infiltrates within a triple negative breast cancer classifier", 2016 San Antonio Breast Cancer Symposium, December 2016, incorporated herein by reference in its entirety).

[0128] The present disclosure provides technologies for improved cancer subtype classification and, moreover, provides technologies for predicting tumor responsiveness to particular immunotherapies (e.g., to immune checkpoint inhibitor therapies).

[0129] Among other things, the present disclosure (1) provides technologies for establishing small gene sets (i.e., involving about 10 to about 50, or preferably about 10 to about 30 genes) whose expression patterns accurately subtype tumor samples; (2) provides an insight that consideration of *including* mesenchymal (M) subtype signature *and also* immunomodulatory (IM) status, and in certain embodiments including *each* of (a) M subtype, (b) mesenchymal-stem-like (MSL) subtype, and also (c) IM status, permits effective assessment of likely responsiveness to immunotherapies such as immune checkpoint inhibitor therapies; and (3) that assessment of IM status (as a positive predictor of responsiveness) vs M and/or MSL status (as a negative predictor of responsiveness) using the provided small gene set effectively determines likelihood of tumor responsiveness to immune checkpoint inhibitor therapy.

[0130] The present disclosure exemplifies provided technologies in the context of both triple negative breast and non -small cell lung cancer, and teaches its applicability across cancers (e.g., across solid tumors).

[0131] Among other things, the present disclosure solves certain problems associated with tumor subtyping and/or predicting such responsiveness. For example, in a study of gene signatures associated with tumor inflammation and epithelial-to-mesenchymal

transition in lung cancer, Thompson *et al.* described "Disagreement [that] exists in the literature about the relationship of inflammatory genes to the mesenchymal phenotype". *See* Thompson *et al.,* "Gene signatures of tumor inflammation and epithelial-to-mesenchymal transition (EMT) predict responses to immune checkpoint blockade in lung cancer with high accuracy", *Lung Cancer*, 139, 2020, incorporated herein by reference. Specifically, Thompson *et al.* noted that other researchers (Chae *et al*, "Epithelial mesenchymal transition (EMT) signature is inversely associated with T-cell infiltration in non-small cell lung cancer (NSCLC)", *Sci. Rep.*, 8, 2018) had "found that a more mesenchymal signature was associated with lower T cell gene expression in NSCLC" which they contrasted with their own data, which they described as "showing that tumors with higher inflammation scores had higher (more mesenchymal) EMT scores", which they observed was "similar" to reports from yet others (Lou *et al*, "Epithelial-mesenchymal transition is associated with a distinct tumor microenvironment including elevation of inflammatory signals and multiple immune checkpoints in lung adenocarcinoma", *Clin. Cancer Res.*, 22, 2016, and Chen *et al.*, "Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression", *Nat. Commun.*, 5, 2014, each of which is incorporated herein by reference.

[0132] The present disclosure provides technologies that define small gene sets effective for tumor subtype classification, and furthermore for comparison of "M" and/or "MSL" vs "IM" status, while establishing benefit of a combined "positive"/"negative" assessment approach, considering both IM (positive) and M and/or MSL (negative) features, for determining tumor responsiveness to immunomodulation therapy such as immune checkpoint inhibitor therapy.

[0133] Among other things, the present disclosure provides technologies for assigning an immuno-oncology (IO) score to a tumor sample by assessing both the negative predicting features of the M subtype and the positive predicting features of the IM status through gene expression analysis of a small set (e.g., about 10 to about 50, or preferably about 10 to about 30) of genes. In some embodiments, the present disclosure provides technologies for assigning an IO score to a tumor sample by assessing both the negative predicting features of the MSL subtype and the positive predicting features of the IM status through gene expression analysis of a small set (e.g., about 10 to about 50, or preferably about 10 to about 30) of genes. In some embodiments, the present disclosure provides

technologies for assigning an IO score to a tumor sample by assessing both the negative predicting features of the M and MSL subtype and the positive predicting features of the IM status through gene expression analysis of a small set (e.g., about 10 to about 50, or preferably about 10 to about 30) of genes. The present disclosure exemplifies effectiveness of provided strategies, including by development of a 27-gene panel established to be effective for tumor subtype classification and characterization of likely responsiveness (or resistance) as described herein.

[0134] Importantly, the present disclosure demonstrates that, unlike previous cancer subtyping and scoring methods, provided technologies can develop small gene sets (e.g., including about 10 to about 50, or even about 10 to about 30 genes) effective to classify tumor subtypes and furthermore to predict tumor responsiveness across different cancers. Indeed, literature reports have declared that "it is improbable to predict wide-ranging clinical benefits without using a wide set of biomarkers". *See*, Fares *et al.* "Mechanisms of Resistance to Immune Checkpoint Blockade", *ACSO Educational Book*, 39, 2019, incorporated herein by reference. The present disclosure demonstrates surprising success in this area of acknowledged challenge.

[0135] Without wishing to be bound by any particular theory, the present disclosure provides an insight that consideration of conditions of the tumor microenvironment may contribute to successful development of predictive models as described herein. For example, in some embodiments, the present disclosure teaches potentially excluding from gene sets utilized for assessment of tumor subtype and/or responsiveness to immunomodulation therapy (e.g., to immune checkpoint inhibitor therapy) as described herein genes, such as those that encode for the TGF-β family of proteins (e.g. TGFB1), that participate broadly in multiple cellular functions. In some embodiments, the present disclosure teaches that focus on more downstream genes and/or on genes involved in features of the tumor microenvironment.

[0136] Among other things, the present disclosure therefore provides a medically useful tool for classifying tumor samples and/or for predicting likely prognosis and/or predicting likely responsiveness of the tumor(s) to particular therapeutic modalities and/or treatment regimens, and specifically to immunomodulation therapy treatments such as immune checkpoint inhibitor therapy when appropriate or to therapies which act upon the

tumor microenvironment to enhance immunogenicity and improve responsiveness to immunomodulation therapy treatments such as immune checkpoint inhibitor therapy when appropriate.

[0137] In some embodiments, the present disclosure provides kits for detecting expression of gene expression signatures in or from tumor samples, as well as technologies for selecting, monitoring, and/or adjusting therapies administered.

[0138] Alternatively or additionally, in some embodiments, the present disclosure provides technologies for developing small gene sets (e.g., including about 10 to about 50, or even about 10 to about 30 genes) and/or for establishing their effectiveness in classifying tumor samples and/or in predicting likely prognosis and/or responsiveness to particular therapeutic modalities and/or treatment regimens, and specifically to immunomodulation therapy treatments such as immune checkpoint inhibitor therapy.

Immunomodulation Therapy

[0139] As noted herein, the present disclosure provides insights relating to responsiveness of particular tumors (i.e., patients) to particular therapy, and specifically to immunomodulation therapy. Without wishing to be bound by any particular theory, the present disclosure teaches that consideration of particular markers (e.g., those reflective of a mesenchymal and/or mesenchymal-like state, and/or those reflective of immunological activity within the tumor microenvironment) together can distinguish between and among tumors that (a) are in an immunologically "cold" state and are unlikely to respond to immunomodulation therapy; (b) are in an immunologically "hot" state and are likely to respond to immunomodulation therapy; and (c) are in an immunologically "poised" state, susceptible to transition to a "hot" state (e.g., by exposure to a particular treatment or therapy which may, in some embodiments, be or comprise immunomodulation therapy or may be or comprise other therapy, for example that may enhance immunogenicity for subsequent treatment by immunomodulation therapy).

[0140] Among other things, the present disclosure provides an insight that consideration of "intrinsic" vs "extrinsic" features characteristic of an immunological state can provide useful and valuable information, including as is relevant to therapy. For example, in some embodiments, assessment of immunological state can consider: (i)

properties of a tumor itself; and/or (ii) properties of surrounding non-malignant, stromal tissue. In some embodiments, properties according to (i) may be referred to as intrinsic features and may correlate to the M or mesenchymal subtype. In some embodiments, properties according to (ii) may be referred to as extrinsic features and correlates to the MSL or mesenchymal-stem-like subtype. Without wishing to be bound by any particular theory, the present disclosure proposes, in some embodiments, that intrinsic and extrinsic features work together (e.g., synergistically with each other) to promote immune escape, *e.g.*, where an immune system loses its capability adequately impede the growth of a tumor (*See*, Seliger, B. and C. Massa, Immune Therapy Resistance and Immune Escape of Tumors. Cancers, 2021. 13(3): p. 551; Xiong, J., H. Wang, and Q. Wang, Suppressive Myeloid Cells Shape the Tumor Immune Microenvironment. Advanced Biology, 2021. 5(3): p. 1900311; Xiao, Y. and D. Yu, Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther, 2021. 221: p. 107753, each of which is incorporated herein by reference in its entirety); in some embodiments, according to the present disclosure, assessment of such features can therefore inform likelihood that the relevant tumor will or will not be responsive to a particular therapy..

[0141] In some embodiments, intrinsic features of an immunologically "cold" state may include one or more of (i) an ability to evade recognition by the immune system (*e.g.*, through mutations in tumor DNA); and (ii) having undergone epithelial to mesenchymal transition (*See*, Seliger, B. and C. Massa, Immune Therapy Resistance and Immune Escape of Tumors. Cancers, 2021. 13(3): p. 551; McGranahan, N., et al., Allele-Specific HLA Loss and Immune Escape in Lung Cancer Evolution. Cell, 2017. 171(6): p. 1259-1271.e11, each of which is incorporated herein by reference in its entirety).

[0142] In some embodiments, extrinsic features of an immunologically "cold" state may include one or more of (i) increased presence of immune-suppressive cells (*e.g.*, certain types of CAFs, M2 macrophages, N2 neutrophils); (ii) increased vascularization of the tumor microenvironment (TME); and (iii) increased expression of one or more extracellular matrix genes (ECM) (*See*, Seliger, B. and C. Massa, Immune Therapy Resistance and Immune Escape of Tumors. Cancers, 2021. 13(3): p. 551; Desbois, M. and Y. Wang, Cancer-associated fibroblasts: Key players in shaping the tumor immune microenvironment. Immunological Reviews, 2021. 302(1): p. 241-258, each of which is incorporated herein by reference in its entirety).

[0143] In some embodiments, tumors classified as having high expression levels of genes with an M subtype (*e.g.*, a tumor with M subtype) may secrete factors that recruit cancer-associated fibroblasts (CAFs) to the stroma. In some embodiments, CAFs may secrete factors such as fibroblast growth factor (FGF) and Wnt Family Member 3A (Wnt-3a) to promote proliferation in cancer cells and stromal derived factor-1 (CXCL12) to increase metastatic potential.

[0144] In some embodiments, immunosuppression in the stroma (*e.g.*, in a tumor with MSL subtype) may limit types of immune cells targeting a tumor. In some embodiments, a tumor with M or MSL subtype may appear non-antigenic to one or more immune cells.

[0145] In some embodiments, the present disclosure provides technologies for administering (and/or monitoring and/or refraining from administering) certain therapies, e.g., an immunomodulatory therapy such as ICI therapy. Alternatively or additionally, in some embodiments, the present disclosure provides technologies for administering (and/or monitoring and/or refraining from administering) an immunomodulatory therapy such as T-cell therapy (e.g., CAR-T therapy) and/or vaccine therapy (e.g., neoantigen vaccination). Still further alternatively or additionally, in some embodiments, the present disclosure provides technologies for administering (and/or monitoring and/or refraining from administering) one or more combination therapies including, for example a combination of a non-immunomodulatory therapy (e.g., chemotherapy, radiation therapy, surgery, etc) with an immunomodulation therapy (e.g., ICI therapy, T cell therapy, vaccination, etc). Indeed, in some embodiments, treatment with another therapy may sensitize or otherwise enhance responsiveness of tumor to immunomodulation therapy, e.g., by enhancing the immunogenicity state of the tumor, as may in some embodiments be assessed, for example, as described herein.

Immune Checkpoint Inhibitory Therapy

[0146] Recent research has shown that malignant cells can escape immunosurveillance through different mechanisms, including activation of immune checkpoint pathways that can suppress immune responses. T cells typically target tumor cells through two main mechanisms: 1) antigen-specific signals mediated by T cell receptors or 2) antigen-nonspecific signals through co-signaling receptors (see Figure 1). Cellular expression of co-signaling receptors can either activate T-cell response (co-stimulatory

receptors) or reduce T cell response (co-inhibitory receptors). *See,* for example, Chen *et al.* "Molecular mechanisms of T cell co-stimulation and co-inhibition" *Nat. Rev. Immunol.*, 13, 2013, incorporated herein by reference in its entirety.

[0147] Tumor cells that express co-inhibitory receptors are able to "hide" as functional host tissue to evade immune recognition and attack. Inhibitory factors, e.g. antibodies, that bind to co-inhibitory immune checkpoints can interrupt these pathways and promote an immune response targeting tumor cells. These immune checkpoint inhibitors (ICIs) can target various immune checkpoints, including, for example, CTLA-4 (CD 152), PD-1, PD-L1, BTLA, VISTA, TIM-3, LAG3, CD47, and TIGIT, as well as their respective binding partners. ICIs can also target various co-stimulatory molecules, including, for example, CD137, OX40, and GITR. *See,* for example, Advani *et al.* "CD47 Blockage by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma" *N. Engl. J. Med.*, 379, 2018; Anderson *et al.*, "Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells" *Science*, 318, 2007; Fourcade *et al.* "CD8(+) T cells specific for tumor antigens can be rendered dysfunctional by the tumor microenvironment through upregulation of the inhibitory receptors BTLA and PD-1" *Cancer Res.*, 72, 2012; Gough *et al.* "Adjuvant therapy with agonistic antibodies to CD134 (OX40) increases local control after surgical or radiation therapy of cancer in mice" *J. Immunother.*, 33, 2010; Hernandez-Chacon *et al.*, "Costimulation through the CD137/4-1BB pathway protects human melanoma tumor-infiltrating lymphocytes from activation-induced cell death and enhances antitumor effector function" *J. Immunother.*, 34, 2011; Lines *et al.* "VISTA is an immune checkpoint molecule for human T cells" *Cancer Res.*, 74, 2014; Ngiow *et al.* "Anti-TIM3 antibody promoters T cell IFN-gamma-mediated antitumor immunity and suppresses established tumors" *Cancer Res.*, 71, 2011; Schaer *et al.* "Anti-GITR antibodies-potential clinical applications for tumor immunotherapy" *Curr. Opin. Investig. Drugs*, 11, 2010;Wang *et al.* "VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses" *J. Exp. Med.*, 208, 2011; Watanabe *et al.* "BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1" *Nat. Immunol.*, 4, 2003; Woo *et al.* "Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape" *Cancer Res.*, 72, 2012; Vaddepally *et al.* "Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with

the Level of Evidence" *Cancers*, 12, 2020, each of which is incorporated herein by reference in its entirety.

[0148] Immunotherapies using immune checkpoint inhibitors (ICIs) have shown great promise in the treatment of various cancers, particularly including cancers characterized by solid tumors. Indeed, ICI therapy is standard of care for lung cancer, breast cancer, and certain other solid tumor types (*See*, Tang *et al.*, "Comprehensive analysis of the clinical immuno-oncology landscape", *Ann. Oncol.*, 29, 2018; *see also,* Vaddepally *et al.*, " Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCNN Guidelines with the Level of Evidence", *Cancers (Basel)*, 12, 2020, each of which is incorporated herein by reference in its entirety). Although ICIs are able to improve clinical outcomes for patients with a variety of solid tumors, only a small subset of patients respond (*See*, Havel *et al.*, "The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy", *Nat Rev Cancer*, 19, 2019; *see also*, Marshall *et al.*, "Immuno-Oncology: Emerging Targets and Combination Therapies", *Front Oncol*, 8, 2018, each of which is incorporated herein by reference in its entirety). Moreover, ICIs can cause immune-related adverse events, some of which are clinically serious and potentially life-threatening (*See,* Postow *et al.*, "Immune-Related Adverse Events Associated with Immune Checkpoint Blockade", N. Engl. J Med, 378, 2018; *see also,* Puzanov *et al.*, "Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group", *J Immunother Cancer*, 5, 2017, each of which is incorporated herein by reference in its entirety). The present disclosure addresses a need to identify patients who are more likely to benefit from ICI therapy with minimal toxicity.

[0149] There are currently a number of FDA-approved ICIs on the market that target PD-1, PDL-1, and CTLA-4 immune checkpoints (see Table 2 below). Immunomodulation therapy treatment with these ICIs has been approved and tested for a variety of indications, with scoring guidelines also available based upon the publicly available National Comprehensive Cancer Network (NCCN) scoring guidelines (see Tables 3-9 below). Dosage and usage information for each drug is also available within corresponding, publicly available FDA prescribing information.

[0150] Table 2: FDA-Approved ICIs

Drug Name	Target	Initial FDA Approval Date	Dosage information
ipilimumab	CTLA-4	2011	See page 1 of FDA prescribing information
nivolumab	PD-1	2014	See page 1 of FDA prescribing information
pembrolizumab	PD-1	2014	See pages 1-3 of FDA prescribing information
cemiplimab-rwlc	PD-1	2018	See page 1 of FDA prescribing information
atezolizumab	PDL-1	2016	See page 1 of FDA prescribing information
avelumab	PDL-1	2017	See page 1 of FDA prescribing information
durvalumab	PDL-1	2017	See page 1 of FDA prescribing information

[0151] Table 3: Ipilimumab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	NCCN Guideline Category
Surgically unresectable, stage 3 or 4 malignant melanoma, previously treated or untreated in adults and pediatric patients > 12 years	2A
BRAF V600 wild-type unresectable or metastatic melanoma	1
In combination with nivolumab for unresectable or metastatic melanoma across BRAF status	1
Adjuvant treatment of cutaneous melanoma stage IIIA, IIIB, and IIIC after complete resection along with total lymphadenectomy	2A
In combination with nivolumab, for patients with previously untreated advanced renal cell carcinoma (RCC), relapse and stage IV, with intermediate- or poor-risk RCC, regardless of PD-L1 This combination can be used in relapse and stage IV RCC patients as a subsequent therapy after patients have undergone TKI, VEGF or mTOR therapy	1 2A
In combination with nivolumab for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan in adults and pediatric patients >12 years	2A

[0152] Table 4: Nivolumab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**
Unresectable or metastatic melanoma cancer progressed following treatment with ipilimumab, or a BRAF inhibitor in BRAF mutation-positive patients	1
In combination with ipilimumab for unresectable or metastatic melanoma across BRAF status	1
Lymph node-positive or metastatic melanoma patients who had undergone complete resection	1
Current first-line systemic therapy in patients with recurrent or metastatic melanoma regardless of BRAF V600-mutation status	1
Second line regardless of the histological subtype in non-small-cell lung cancer (NSCLC) in patients who showed progression despite the platinum-based therapy	1
Small-cell lung cancer (SCLC) patients who progressed on platinum-based therapy and at least one other line of therapy	2A
Advanced renal cell cancer (RCC) with prior anti-cancer therapy (mTOR)	1
In combination with ipilimumab, for patients with previously untreated advanced RCC, relapse and stage IV, with intermediate- or poor-risk RCC, regardless of PD-L1 This combination can be used in relapse and stage IV RCC patients as a subsequent therapy after patients have undergone TKI, VEGF or mTOR therapy	1 2A
Hodgkin's lymphoma that has progressed or relapsed after auto-HSCT and post-transplantation brentuximab vedotin therapy, or three or more lines of systemic therapy that includes auto-HSCT	2A
Recurrent or metastatic squamous cell cancer of head and neck (SCCHN) that hasprogressed on or after platinum-based therapy (non-nasopharyngeal—Category 1*; nasopharyngeal—Category 2B*)	1* 2B*
Surgically unresectable or metastatic urothelial cancer	A
In combination with ipilimumab for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan in adults and pediatric patients > 12 years	2A
Hepatocellular carcinoma (HCC) previously treated with sorafenib	2A

[0153] Table 5: Pembrolizumab. Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**
Metastatic melanoma refractory to ipilimumab and BRAF inhibitor with BRAF mutation	2A
Previously untreated advanced melanoma regardless of BRAF mutation status	2A
Adjuvant treatment of lymph node(s)-positive melanoma following complete resection	1
Metastatic melanoma with limited resectability, if there is no disease after resection, as an adjuvant therapy	2A
Metastatic non-small-cell lung cancer (NSCLC) that progressed after platinum-based therapy or, if appropriate, targeted therapy (EGFR/ALK mutation) and positive for PDL-1	1
First-line treatment in patients with metastatic non-small-cell lung cancer with high PDL-1 expression (50%) but no EGFR or ALK mutation	1 2B if PDL-1 1-49%
First-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK mutation, irrespective of PDL-1 expression	1
First-line treatment in metastatic squamous NSCLC in combination with carboplatin with paclitaxel/nab-paclitaxel regardless of PD-L1 status	1
First-line monotherapy in patients with stage 3 NSCLC who are not candidates for surgical resection as well as chemoradiation or metastatic NSCLC with PDL-1 expression 1% and no EGFR or ALK mutation	1
For recurrent or metastatic squamous cell cancer of head and neck (HNSCC) patients with progression on standard platinum-based therapy (non-nasopharyngeal—Category 1*; nasopharyngeal and PD-L1 positive—Category 2B*)	1* 2B*
First-line therapy for patients with metastatic or unresectable, recurrent HNSCC either as monotherapy in patients whose tumor expresses PD-L1 (combined positive score 1%) or in combination with platinum and fluorouracil	2A
Refractory adult and pediatric classical Hodgkin's lymphoma	2A
Unresectable or metastatic urothelial cancer with progression on or after platinum-based therapy including in the adjuvant setting	2A
First-line therapy for unresectable or metastatic urothelial cancer patients who are ineligible for cisplatin-containing chemotherapy	2A
Locally advanced or metastatic urothelial carcinoma patients who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 > 10%, or in patients who are	2A

not eligible for any platinum-containing chemotherapy regardless of PD-L1 status	
Unresectable or metastatic solid tumor patients with biomarker MSI-H or dMMR who have progressed after first-line therapy without satisfactory alternative therapy, irrespective of the location of the primary tumor	2A
Third-line therapy for recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma patients with PD-L1 expression (combined positive score 1%) who have progressed on or after two or more prior lines of therapy including fluoropyrimidine and a platinum-based regimen and, if appropriate, HER2/neu-targeted therapy	2A
Esophageal (squamous and adenocarcinoma) and EGJ adenocarcinoma, subsequent therapy for MSI-H or dMMR tumors; Category 2B for second-line therapy with PD-L1 expression 10% Category 2B for third-line or subsequent therapy	2A
Recurrent or metastatic cervical cancer progressing on or after chemotherapy and positive for PDL-1	2A
Refractory or relapsed primary mediastinal large B-cell lymphoma (PMBCL)	2A
HCC patients who had previously been treated with sorafenib	2B
First-line therapy for adult and pediatric patients with recurrent or locally advanced or metastatic Merkel cell carcinoma (MCC)	2A
Combination with axitinib (Inlyta) as first-line treatment for patients with metastatic renal cell cancer (RCC) (poor and intermediate risk—Category 1*; favorable risk—Category 2A*)	1* 2A*

[0154] Table 6: Cemiplimab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**
Metastatic or locally advanced cutaneous squamous cell carcinoma who are not the candidate for curative surgery or radiation	2A

[0155] Table 7: Avelumab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**

Metastatic Merkel cell carcinoma of adults and pediatric patients > 12 years including those who have not received prior chemotherapy	2A
Locally advanced or metastatic urothelial carcinoma patients whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy	2A
Avelumab in combination with axitinib (Inlyta) for the first-line treatment of patients with advanced renal cell carcinoma (RCC) alternative to pembrolizumab (which is the preferred agent)	2A

[0156] Table 8: Durvalumab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**
Locally advanced or metastatic urothelial carcinoma patients with disease progression during or following platinum-containing chemotherapy, or whose disease has progressed within 12 months of receiving platinum-containing chemotherapy neoadjuvant or adjuvant, alternative to preferred agent pembrolizumab	2A
Stage III non-small-cell lung cancer (NSCLC) patients for surgically unresectable tumors and whose cancer has not progressed after treatment with chemoradiation	1

[0157] Table 9: Atezolizumab Indications and NCCN Guidelines. Adapted from Vaddepally *et al.*

Indications	**NCCN Guideline Category**
Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy, or within 12 months of receiving platinum-containing chemotherapy as neoadjuvant or adjuvant therapy	2A
Locally advanced or metastatic urothelial carcinoma patients who are not candidates for platinum-based chemotherapy regardless of PD-L1 expression	2A
Metastatic non-small-cell lung cancer (NSCLC) patients with disease progression during or following platinum-containing chemotherapy who have progressed on an appropriate FDA-approved targeted therapy	1
In combination with bevacizumab, paclitaxel and carboplatin for initial treatment of people with metastatic non-squamous non-small-cell lung cancer (NSCLC) with no EGFR or ALK	1

In combination with carboplatin and etoposide, for the initial treatment of adults with extensive-stage small-cell lung cancer	1
In combination with paclitaxel for adults with unresectable locally advanced or metastatic triple-negative breast cancer in people whose tumors express PD-L1	2A

[0158] Combinations of ICI therapy with targeted therapeutics such as small molecule immunomodulators (e.g. colony stimulating factor-1 receptor (CSF-1R) and focal adhesion kinase (FAK)) and anti-angiogenesis (e.g. VEGF) inhibitors that act upon the tumor microenvironment are being investigated to improve durable response rates. *See,* for example, Osipov *et al.* "Small molecule immunomodulation: the tumor microenvironment and overcoming immune escape" *J Immunother Cancer*, 7: 224, 2019; Ciciola *et al.* "Combining Immune Checkpoint Inhibitors with Anti-Angiogenic Agents" *J Clin Med.*, 9(3): 675, 2020.

[0159] Table 10: Recent FDA Approvals for ICI therapy in combination with standard of care chemotherapy or targeted therapeutics. Adapted from cancerresearch.org/immunotherapy/timeline-of-progress.

Description	**FDA Approval Date**
The FDA approved the combination of atezolizumab (Tecentriq), a PD-L1 checkpoint inhibitor, and bevacizumab (Avastin), a VEGF-A monoclonal antibody, for the treatment of patients with previously untreated hepatocellular carcinoma (HCC), the most common form of liver cancer.	May 29, 2020
The FDA approved durvalumab (Imfinzi), a PD-L1 checkpoint inhibitor immunotherapy, as a the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with standard-of-care chemotherapy.	March 30, 2020

[0160] Table 11: Examples of Clinical Trials utilizing targeted therapeutics to act upon the TME to improve immunomodulation. Adapted from Osipov *et al.* and Ciciola *et al.*

Description	**NCI Identifier**
Evaluation of Safety and Activity of an Anti-PDL1 Antibody (DURVALUMAB) Combined With CSF-1R TKI (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers	NCT02777710

A Study of ARRY-382 in Combination With Pembrolizumab for the Treatment of Patients With Advanced Solid Tumors	NCT02880371
Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors	NCT02829723
Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)	NCT02758587
ROCKIF Trial: Re-sensitization of Carboplatin-resistant Ovarian Cancer With Kinase Inhibition of FAK	NCT03287271
Defactinib Combined With Pembrolizumab and Gemcitabine in Patients With Advanced Cancer	NCT02546531
Study of Safety, Efficacy and Pharmacokinetics of CT-707 in Patients With ALK-positive Non-small Cell Lung Cancer	NCT02695550
Study of Pembrolizumab With or Without Defactinib Following Chemotherapy as a Neoadjuvant and Adjuvant Treatment for Resectable Pancreatic Ductal Adenocarcinoma	NCT03727880
Phase I/II Study of Nivolumab and Ipilimumab Combined With Nintedanib in Non Small Cell Lung Cancer	NCT03377023
Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Deficient DNA Mismatch Repair Metastatic Colorectal Cancer, the COMMIT Study	NCT02997228
Study of First-line Pembrolizumab (MK-3475) With Lenvatinib (MK-7902/E7080) in Urothelial Carcinoma Cisplatin-ineligible Participants Whose Tumors Express Programmed Cell Death-Ligand 1 and in Participants Ineligible for Platinum-containing Chemotherapy (MK-7902-011/E7080-G000-317/ LEAP-011)	NCT03898180

T Cell Therapy

[0161] Among the immunomodulation therapies being developed and/or utilized to treat certain cancers are therapies that involve administration of populations of cells (typically T cells) that have been expanded *ex vivo*. Adoptive T cell therapies, including CAR-T therapies, have shown great promise in certain contexts. *See,* for example, Hinrichs & Restifo *Nat Biotechnol* 31:999, 2013; Newick et al *Oncolytics* 2016; Zhang & Wang doi.org/10.1177/1533033819831068, 2019. The present disclosure provides technologies that can improve effectiveness of T cell therapies, by providing tumor characterization technologies, and establishing parameters (e.g., correlations) indicative of tumor responsiveness to immunomodulation.

[0162] Chimeric antigen receptor (CAR)-T-cell therapy is a form of immunomodulation therapy that repurposes T cells to express specific protein components able to recognize surface-exposed antigens on cancer cells. Once bound to a target, the

reprogrammed T cells activate and proceed to destroy the tumor cells through various mechanisms, including, e.g., stimulated cell expansion and enhanced cytokine production (*See,* Tang *et al.* "Therapeutic potential of CAR-T cell-derived exosomes: a cell-free modality for targeted cancer therapy", *Oncotarget*, 6, 2015, incorporated herein by reference in its entirety). T cells may be harvested from a patient by leukapheresis and enriched through various positive and negative selection methods, including, e.g., elutriation, *ex vivo* expansion. Isolated T cell populations can be engineered *ex vivo* to express necessary CAR machinery, including, e.g., tumor-binding regions, which are often optimized to target cancer-specific surface antigens. These reprogrammed T cells can be further enriched to select for viable cells expressing the desired CAR activation and binding domains, e.g. through flow cytometry methods, including fluorescence-activated cell sorting (FACS).

[0163] Engineered CAR-T cells typically comprise an extracellular domain for antigen recognition, which is connected to one or more intracellular signaling domains to control T-cell activation. An antigen recognition domain may consist of one or more antibody components, e.g. the variable heavy and variable light chains of an antibody, which are fused through a peptide spacer. A peptide spacer may be further linked to an intracellular signaling domain, such an immune-receptor-tyrosine-based-activation-motif (ITAM) protein. Recent work has shown that inclusion of one or more co-stimulatory domains can lead to improved T-cell activation, among other things (see Figure 2). CAR-T cells may be harvested from a patient for self-use or collected from a healthy, allogeneic donor for use in a patient. *See*, Feins *et al.* "An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer", *Am J Hematol.* 94, 2019, incorporated herein by reference in its entirety.

[0164] There are several FDA-approved CAR-T therapies currently available for treatment of certain B-cell lymphomas. These therapies include tisagenlecleucel (Kymriah™), axicabtagene ciloleucel (Yescarta™), and brexucabtagene autoleucel (Tecartus™). Dosage and usage information for each therapy is available within corresponding, publicly available FDA prescribing information.

Neoantigen Vaccine Therapy

[0165] Neoantigens are cancer-specific epitopes that arise as a result of unique mutations within tumor cells. A variety of therapeutic modalities have been developed to

trigger or enhance a patient's immune response to neoantigens that arise in his/her tumor. For example, a variety of prediction algorithms and/or characterization regimes have been developed to identify those neoantigens most likely to support a robust patient immune response, and vaccine technologies that administer peptides containing neoantigens, nucleic acids (e.g., DNA or RNA) that encode them, dendritic cells that display them, T-cells that target them, etc. have been the subject of many studies (*See*, for example, Figure 3 below and Peng *et al.*, "Neoantigen vaccine: an emerging tumor immunotherapy", *Mol. Cancer*, 18, 2019; *see also*, Chu *et al. Theranostics* 8:4238, 2018, each of which is incorporated herein by reference in its entirety).

Combination Therapy

[0166] In some embodiments, the present disclosure relates to administration (and/or monitoring, and/or withholding) of one or more combination therapies, typically including at least one immunomodulation therapy.

[0167] For example, according to the present disclosure, in some embodiments, administration of one therapy may increase responsiveness to another therapy (e.g., to an immunomodulation therapy).

[0168] Moreover, those skilled in the art are aware that combination therapy, including combinations of immunomodulatory therapies, is often recommended for cancer therapy.

[0169] For example, combination of ICIs with CAR-T therapy has been proposed, among other things to address up-regulation of certain immune checkpoints that has been shown to correlate with tumor resistance to CAR-T cell therapy. (*See*, Beatty *et al.*, "Chimeric antigen receptor T cells are vulnerable to immunosuppressive mechanisms present within the tumor microenvironment", *Oncoimmunology*, 3, 2014, incorporated herein by reference in its entirety). Alternatively or additionally, combination of T cell and ICI therapy may address T-cell exhaustion reported with certain adoptive T cell (e.g., CAR-T therapies) after initial activation and lysis of tumor cells (See Figure 4). Initial administration of CAR-T therapy followed by ICI treatment has been proposed as a strategy to induce reactivation of CAR-T function and produce functional therapeutic persistence (*See*, Grosser *et al.*, "Combination Immunotherapy with CAR T Cells and Checkpoint

Blockade for the Treatment of Solid Tumors", *Cancer Cell*, 36, 2019, incorporated herein by reference in its entirety).

[0170] Additionally, pre-clinical studies have shown that combination therapies comprising an anti-CTLA-4 antibody and a tumor antigen-specific vaccine led to increased survival in a tumor cell model (*See,* Linch *et al.*, "Combination OX40 agonist/CTLA-blockade with HER2 vaccination reverses T-cell anergy and promotes survival in tumor-bearing mice", *PNAS*, 2016, incorporated herein by reference in its entirety). Various reports recommending combination of ICI therapy with neoantigen therapy have also been described. *See,* for example, Fotin-Mleczek et al. J Gene Med. 14(6):428-39; see also WO2014/127917.

[0171] In some embodiments, provided technologies are applied to combination therapy with at least one immunomodulation therapy and at least one other therapy (e.g.., chemotherapy, radiation therapy, surgical therapy, etc.).

[0172] For example, certain kinase inhibitors have been shown to enhance ICI therapy effects (*See,* Langdon *et al.*, "Combination of dual mTORC1/2 inhibition and immune-checkpoint blockade potentiates anti-tumour immunity", *Oncoimmunology*, 7, 2018, incorporated herein by reference in its entirety). Various pathways are known to interact with PD-1 signaling, for example, and could be targeted through co-administration of various therapeutics with ICIs (See Figure 5).

[0173] Without wishing to be bound by a particular therapy, the present disclosure provides insights relating to tumor responsiveness that are applicable to various combination therapies. In some embodiments, a combination of one or more immunotherapies and/or anti-tumor therapies may be predicted to be effective when administered to particular patients identified as described herein and/or when administered in a particular order. In some embodiments, the present disclosure provides technologies for selecting patients to receive (or not) such combination therapy, and/or for monitoring such combination therapy (e.g., to assess likely continued effectiveness over time). In some embodiments, effectiveness is assessed or pre predicted relative to a particular comparator therapy (e.g., monotherapy).

IO Scores for Immune Checkpoint Inhibitor Therapy

[0174] Given the importance of ICI therapy, significant effort has been invested in determining predictive biomarkers that can support patient selection for ICI therapy (i.e.,

that can discriminate between patients who are or are not likely to respond if treated with ICI therapy).

[0175] For example, several studies have investigated expression of programmed death-ligand 1 (PD-L1) on tumor cells as a potential predictive biomarker for responsiveness to therapy targeting PD-1 and/or PD-L1. Unfortunately, literature reports that PD-L1 testing does not consistently predict patient benefit from immunomodulation therapy (*See*, Gibney *et al.*, "Predictive biomarkers for checkpoint inhibitor-based immunotherapy", *Lancet Oncol*, 17, 2016; *see also*, Mehnert *et al.*, "The Challenge for Development of Valuable Immuno-oncology Biomarkers", *Clin Cancer Res*, 23, 2017; *see also*, Wojas-Krawczyk *et al.*, "Beyond PD-L1 Markers for Lung Cancer Immunotherapy", *Int J Mol Sci*, 20, 2019, each of which is incorporated herein by reference in its entirety).

[0176] The present disclosure identifies the source of a problem with many such efforts to identify sufficiently effective predictive biomarkers for ICI therapy to be useful in treating patient populations. For example, without wishing to be bound by any particular theory, the present disclosure proposes that complexity of the tumor-immune system interactions that characterize the tumor microenvironment (TME) can complicate efforts to develop such sufficiently effective biomarkers. Within the TME is a complex and dynamic milieu of non-malignant cells that interact with each other and with the tumor cells, affecting tumor growth, invasion and metastasis (*See*, Binnewies *et al.*, "Understanding the tumor immune microenvironment (TIME) for effective therapy", *Nat Med*, 24, 2018; *see also*, Butturini *et al.*, "Tumor Dormancy and Interplay with Hypoxic Tumor Microenvironment", 20, 2019, each of which is incorporated herein by reference in its entirety). The present disclosure proposes that a biomarker which is able to capture the complex interactions and signals of the TME could be more useful in selecting patients who are more likely to benefit from ICI therapies because multiple dimensions are assessed. Assessment of multiple biomarker dimensions can increase sensitivity and accommodate sampling error to produce more accurate results when working with limited sample sizes, e.g. limited amount of tumor tissue sample.

[0177] One approach to developing positive or negative immunomodulatory signatures that might be useful as biomarkers of responsiveness to ICI therapy involved clinical subtyping of triple negative breast cancer (TNBC) patients (*See*, Ring *et al.*, "Generation of an algorithm based on minimal gene sets to clinically subtype triple negative

breast cancer patients", *BMC Cancer*, 16, 2016, incorporated herein by reference in its entirety). In particular, a 101-gene model was developed that classified TNBC into five molecular subtypes, including two basal like (BL1 and BL2), luminal androgen receptor (LAR), mesenchymal (M), and mesenchymal stem-like (MSL); with each of these subtypes further classified by a positive or negative immunomodulatory (IM) signature.

[0178] The present disclosure report provides an insight that TNBC tumors of the M subtype never had a positive IM signature, an observation that can now be appreciated to be consistent with studies showing that the M and IM subtypes are inversely correlated (*See*, Lehmann *et al.*, "Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection", *PLoS One*, 11, 2016; *see also*, Grigoriadis *et al.*, "Mesenchymal Subtype Negatively Associates with the Presence of Immune Infiltrates within a Triple Negative Breast Cancer Classifier", 2016, each of which is incorporated herein by reference in its entirety).

[0179] Without wishing to be bound by any particular theory, the present disclosure proposes that the M and MSL subtypes may be considered antithetical to the IM subtype, with the former subtypes indicating a more quiescent immunological state and the latter indicating an immunologically active state. Additionally, the present disclosure provides an insight that the molecular basis for the M, MSL, and IM subtypes can translate across other solid tumor types based on features of the TME driving this profile. The present disclosure describes technologies that it demonstrates are effective to develop a gene expression algorithm to measure a TME by optimizing a gene set to include those most relevant to the M, MSL, and IM subtypes. Among other things, the present disclosure provides an insight that strategies provided herein can distinguish tumors in an immunologically active (e.g., "hot") state from tumors that are either: 1) in a more quiescent state and unlikely to respond (e.g., "cold") to immunomodulation therapy (e.g. due to increased expression of signatures associated with M and MSL subtypes); and/or 2) in a more quiescent state yet poised to develop or enter an immunologically active state (e.g., to become immunologically "hot"), and therefore likely to respond to immunomodulation therapy (e.g. due to increased expression of signatures associated with IM subtype). These findings may well generalize across tumors (e.g. particularly across solid tumors) and therefore have expanded utility across multiple cancer types.

[0180] The present disclosure exemplifies effectiveness of provided technologies through development and validation of a new 27-gene immuno-oncology algorithm that measures the TME and generates an associated IO score predicting response to immunomodulation therapy treatment. This algorithm was optimized using genes expressed in both quiescent and immunologically active tumors and may be useful in predicting response to immunotherapies.

[0181] In some embodiments, genes assessed in a provided algorithm are associated with a positive IM signature and M and/or MSL subtypes. In particular embodiments, genes with a positive IM signature are characterized as being associated with increased innate immunity (e.g. increased tumor infiltrating lymphocyte and/or natural killer cell levels) and/or adaptive immunity (e.g. increased CD4, CD8 levels) as well as decreased inflammatory characteristics (e.g. decreased neutrophil and/or regulatory T-cell levels). In some embodiments, genes with an M subtype are characterized as having increased expression of one or more of: (1) markers of epithelial-to-mesenchymal transition (EMT); (2) factors (*e.g.*, secreted factors) that may recruit cancer-associated fibroblasts (CAFs) to the stroma. In some embodiments, genes with an MSL subtype are characterized as expressing 1) markers of cancer-associated fibroblasts (CAFs); and 2) markers of mesenchymal stem cells (MSCs), relative to a reference. In some embodiments, inclusion of independent IM, EMT, CAF, and MSC signatures ensures accurate algorithm scoring when making prognostic or predictive responses to immunomodulation therapy.

[0182] Among other things, the present disclosure documents a variety of advantages provided by technologies described herein, including the exemplified small gene set (i.e., 27-gene) immuno-oncology algorithm.

[0183] For example, the ability to define small (e.g., about 10 to about 50, or even about 10 to about 30) gene sets effective to achieve subtype classification and/or responsiveness prediction as described herein dramatically improves commercial feasibility. Moreover, application across cancers provides unusual and unexpected versatility.

[0184] The present disclosure addresses a previously unmet need for improved biomarkers to optimize ICI immunomodulation therapy use in clinical settings. Provided small gene set algorithms (e.g., the exemplified 27-gene immuno-oncology algorithm) can distinguish patients likely to benefit from treatments such as ICIs. Unlike previously described biomarker models, provided technologies measure the immunological state of the

TME as a means to capture the interplay of the patient's immune system and tumor immune evasion. The concept that "tumors are wounds that do not heal" has been used to describe this interplay as the tumor co-ops the wound healing response which encompasses immunosurveillance as well as various aspects of wound healing that appear to be components of tumor maintenance and growth (*See*, Dvorak *et al.*, "Tumors: wounds that do not heal-redux", *Cancer Immunol Res*, 3, 2015, incorporated herein by reference in its entirety). Without wishing to be bound by any particular theory, we propose that provided strategies uniquely capture aspects of immunosurveillance, immunosuppression, and immune evasion as a tumor transitions from a proliferative to a metastatic state, thereby enabling for effective and accurate prediction.

[0185] In some embodiments, provided gene sets and/or algorithms may include and/or focus on genes associated with IM, EMT, CAF, and MSC signatures, optionally in preference to or even with exclusion of other markers (e.g. various growth factors), which can regulate many different cellular functions and provide confounding effects on scoring.

[0186] Another advantage of provided technologies include their ability to utilize data obtained from any of a variety of platforms.

[0187] In some embodiments, technologies described herein have improved predictive power through measurement of each of IM, M, and MSL signatures rather than a single marker group.

[0188] In some embodiments, technologies herein measure each of IM, M, and MSL signatures relative to a reference threshold (*e.g.*, relative to the expression of an alternate set of genes, etc.). In some embodiments, a reference threshold may be determined through analysis of patient data (*e.g.*, relative to patterns of gene expression compared to a pre-determined clinical standard).

[0189] Without wishing to be bound by any particular theory, we propose that, by measuring the immunological state of the TME as a whole, technologies described herein (e.g., including the exemplified 27-gene algorithm) may offer independent and incremental predictive value over the current gold standard biomarkers in the clinic.

Other Features or Characteristics

[0190] In some embodiments, patients assessed or selected (e.g., to receive [or not] particular therapy) in accordance with the present disclosure may be characterized by one or more features and/or characteristics other than (e.g., in addition to) a particular IO score.

[0191] In some embodiments, features and characteristics assessed in accordance with the present disclosure may include one or more of cancer type (e.g. tissue type and/or histology of a tumor), prior lines of treatment received, age, and/or circulating tumor cell burden.

Monitoring Over Time

[0192] In some embodiments, assessment of one or more particular features and/or characteristics (e.g., IO score and/or other characteristics or features) is performed with respect to the same patient at a plurality of different time points. In some embodiments, assessment of one or more particular features and/or characteristics is performed with respect to a particular patient prior to initiation of a particular therapeutic regimen and/or prior to administration of a particular dose of therapy in accordance with such therapeutic regimen.

[0193] For example, in some embodiments, features and/or characteristic assessment(s) is/are performed with respect to a subject or subjects who is receiving, has received, or is a candidate to receive immunomodulation therapy (e.g., with an ICI). In some embodiments, one or more features and/or characteristics is assessed prior to administration of such immunomodulation therapy. In some embodiments, one or more features and/or characteristics is assessed after administration of one or more doses of such immunomodulation therapy. In some embodiments, one or more features and/or characteristics is assessed prior to administration of immunomodulation therapy, and one or more features and/or characteristics is assessed after administration of one or more doses of immunomodulation therapy.

[0194] In some embodiments, different features and/or characteristics may be assessed at different times. In some embodiments, a plurality of features and/or characteristics may be assessed at the same time, and optionally others may be assessed at a different time.

[0195] In some embodiments, one or more features and/or characteristics may be assessed at multiple times. In some embodiments, at least one feature and/or characteristic may be assessed only a single time and one or more other feature(s) and/or characteristic(s) may be assessed at multiple times.

[0196] In some embodiments, provided technologies identify and/or select a subject or subject(s) to whom immunomodulation therapy (e.g. ICI therapy) is administered. Alternatively or additionally, in some embodiments, provided technologies determine timing for administration of one or more doses (which may, in some embodiments, be the same dose or may be different doses) of such immunomodulation therapy. In some particular embodiments, provided technologies determine timing for administration of one or more doses of such immunomodulation therapy relative to one or more doses of another therapy (e.g. chemotherapy).

[0197] In some embodiments, such monitoring of features and/or characteristics over time may inform decisions to continue or modify particular therapy, to interrupt or terminate such therapy, and/or to initiate alternative therapy.

[0198] In some embodiments, without wishing to be bound by any particular theory, assessment of one or more particular features and/or characteristics (e.g., IO score and/or other characteristics or features) affirms a quiescent TME (cold), might indicate that agents which modify or stimulate the immune response through stromal derived signals might be beneficial. Such agents may include, but are not limited to, focal adhesion kinase (FAK) inhibitors, anti TGF-beta, anti angiogenesis (e.g. VEGF, or other multi-targeted receptor tyrosine kinase (RTK) inhibitors and other vascular normalization agents), therapies which target the CD73-adenosine axis (e.g. CD73 inhibitors), other small molecule immunomodulation therapies (e.g. CSF1 Receptor inhibitors), traditional chemotherapies and MTOR inhibitors, bispecific molecules and antibodies, metabolic sequestration agents, and anti TIGIT therapies.

[0199] In some embodiments a low IO score implies that a patient is less likely to respond to ICI therapy and/or that a patient should consider alternate therapies guided by standardized consensus guidelines such as the NCCN guidelines, and or consider treatments offered in the context of an ongoing clinical trial.

Algorithm Development

[0200] Elastic-net regularized linear models were employed to create individual subclassifying models for the BL1, BL2, LAR, MSL, M, and IM subtypes with the subtypes treated as a multinomial variable. The genes utilized for the M and IM subtype classifications with this model were then used to derive a logistic elastic net model on the new data set, minus three genes whose probes had been reassigned between analyses. Strength of association with classification variables was assessed using ten-fold cross validation of the misclassification error. The model threshold for determining the immuno-oncology score (IO score) was determined using the maximum area under the curve (AUC), in contrast to the significance of the correlation method for determining threshold previously described by Ring et al.

[0201] Without wishing to be bound by any particular theory, we note that one differentiated feature of the way this signature was developed was that it was a robust classifier first, and the association of the three features (M, IM, MSL) and their association with ICI (and other immune therapies) discovered later. The robust ability to classify, independent of knowing the biologic significance of classes, allows seamless translation between tumors of different tissue of origin. For example, a classifier can be trained on any gene expression dataset for a cancer of interest (e.g., a solid tumor cancer such as, for example, bladder, breast, cervical, colon, endometrial, kidney, lip, liver, lung (small cell or non-small cell), melanoma, mesothelioma, oral, ovarian, pancreatic, prostate, rectal, sarcoma, thyroid, etc.) and then, after its ability to define, detect, and/or distinguish subtypes of the relevant cancer is established, assess its correlation with responsiveness to particular therapy (e.g., ICI therapy).

[0202] In some embodiments, one or more genes (*e.g.,* genes not included in a classifier or otherwise of interest) can be assessed through an established classifier in order to determine association with one of the three features (M, IM, MSL). For example, in some embodiments, these additional genes of interest can be added to an existing classifier gene set (*e.g.*, the 27 gene set described herein, the 939 gene set described in Example 9) and association with the three features (M, IM, MSL) can be assessed through cluster analysis.

[0203] As described herein, among other things, the present disclosure provides effective classification of M, IM, and MSL features. Those skilled in the art, reading the

present disclosure will therefore appreciate that it permits assessment of association (*e.g.,* correlation) with these classified features. Thus, the present disclosure permits identification and/or characterization of other parameters (*e.g.,* gene expression, gene mutation, protein expression, protein modification, epigenetic modification, *etc.*) that so associate. In some embodiments, such associated features may be or comprise biomarkers (*e.g.,* that may act as a proxy for M, IM and/or MSL features, and therefore, in some embodiments, for likelihood of responsiveness to immunomodulation therapy) that may be detected, for example to characterize subject(s) prior to administration of immunomodulation therapy (*e.g.,* to assess likelihood of responsiveness and/or to select for receipt of immunomodulation therapy and/or for alternative therapy) and/or to monitor subject(s) receiving immunomodulation therapy (*e.g.,* for continued responsiveness and/or for development of resistance). Moreover, those skilled in the art, reading the present disclosure will appreciate that, in some embodiments, technologies provided by the present disclosure, by permitting assessment of association with M, IM, and/or MSL features, can reveal presence and/or development of biological event(s) (*e.g.,* expression and/or mutation of a particular gene or genes) that recommend particular therapy (*e.g.,* targeting a particular expressed or mutated gene) be utilized in addition or as an alternative to immunomodulation therapy.

[0204] The present disclosure demonstrates that use of unsupervised cluster analysis can facilitate identification of distinct biologic phenotypes that may each contribute to classification in any individual tumor specimen. Without wishing to be bound by any particular theory, we propose that this strategy may enhance biologic prediction of response to therapy (e.g., to IO therapy) in some samples; alternatively or additionally, this approach may increase sensitivity, for example by allowing some redundancy in detecting the immune status. For example, as noted above, non-surgical biopsies can be very sparse and stochastic sampling error risks missing relevant biology (e.g. TILS). The redundancy of measuring phenotype from multiple compartments may accommodate sampling error and give accurate results on more sparse specimens.

[0205] For at least these reasons, those skilled in the art will appreciate that features of algorithm development described herein are likely applicable across cancer types (e.g., for solid tumor cancers).

Use

[0206] Technologies provided herein are useful in the assessment of tumor samples and/or for the development and/or validation of tumor subtype classifiers and/or predictors of responsiveness to therapy.

Assessment of Tumor Samples

[0207] For example, with respect to assessment of tumor samples, a tumor sample of interest (e.g., a sample of a solid tumor such as for example, a skin, breast, lung, head and neck, gastric, renal, bladder, urothelial, bone, prostate, thyroid, or pancreatic tumor) may obtained and/or gene expression data from such a sample is obtained for analysis.

[0208] Those skilled in the art are aware of appropriate technologies for obtaining and preparing tumor samples, and for obtaining gene expression data from such samples. For example, gene expression assessment technologies include, but are not limited to microarray analysis, reverse transcription polymerase chain reaction (RT-PCR), Northern blot, reporter genes, real-time PCR, fluorescent *in situ* hybridization, hybridization detection, RNA-sequencing, and serial analysis of gene expression (SAGE).

[0209] In some embodiments, a tumor sample is from a patient prior to initiation of therapy (i.e., the sample is from a patient who has not received therapy to treat the tumor). In some embodiments, a tumor sample is from an excised tumor (e.g., a tumor that has been removed by surgery). In some embodiments, a tumor sample is a tumor biopsy. In some embodiments, the tumor sample is a liquid (e.g., is or comprises one or more of CNS fluid, blood, plasma, pleural fluid, serum, sweat, tears, urine, etc.; most typically blood, plasma, and/or serum.

[0210] In some embodiments, a tumor sample is from a patient who is receiving therapy (e.g., anti-cancer therapy which, in some embodiments, does not include and/or has not included ICI therapy and in other embodiments is or comprises ICI therapy).

[0211] In some embodiments, as discussed above, multiple tumor samples may be obtained from a patient (and/or from a particular tumor in a patient) over time, for example, to assess effectiveness of therapy and/or to assess continued likely responsiveness to therapy.

[0212] In some embodiments, one or more therapies(*e.g.*, ICI therapy) are administered (or continued) for patients determined to have an IO score indicative of likely responsiveness as described herein. In some embodiments, one ore more therapies (*e.g.*, ICI

therapy) are withheld, or additional or alternative therapies are administered for patients determined to have an IO score indicative of likely non-responsiveness, or of a decrease in likely responsiveness over time. In some embodiments, additional or alternative therapies may comprise therapies associated with one or more genes, gene mutations and/or gene pathways identified (*e.g.,* as described herein or otherwise) to be associated with a reduced IO score (*e.g.*, associated with M or MSL classifiers). In some embodiments, IO score is re-assessed after administration of additional or alternative therapies. In some embodiments, IO score is monitored over time, for example to determine whether likely responsiveness to one or more therapies (*e.g.*, ICI therapy) may change.

Algorithm Development and/or Assessment

[0213] As discussed herein, the present specification provides technologies for algorithm development and/or assessment. Included within such provided technologies are systems for validating and/or otherwise characterizing tumor subtype classifiers and/or predictors of responsiveness to therapy, for example by comparison with those described herein.

[0214] As described herein, the present disclosure documents effective classification of tumor (e.g., solid tumor, e.g., TNBC tumor) subtypes; provided classification technologies (e.g., the small gene set model described herein) provide a reference relative to which alternative embodiments or strategies can be compared; in some embodiments, the present disclosure thus provides methods that involve such comparison.

[0215] In some embodiments, technologies provided herein are useful for the determination of patterns of gene expression (*e.g.*, identification of genes whose quantitative variation in expression may vary in similar ways across large sample sets, also referred to herein as metagenes). In some embodiments, metagenes may be used as classifiers to measure sample physiology by identifying physiologically significant subsets of samples (*e.g.*, acting as diagnostics to support clinical decision making, including treatment selection). In some embodiments, one or more genes within a metagene group may be used to measure physiology. In some embodiments, two or more genes within a metagene group may be used to measure physiology. In some embodiments, three or more genes within a metagene group may be used to measure physiology. In some embodiments, a selected number of genes within a metagene group that is representative of the group as a whole may be used to measure physiology.

[0216] Analogously, the present disclosure documents effective prediction of likely tumor responsiveness to therapy; these technologies also provide a reference relative to which alternative embodiments or strategies can be compared; in some embodiments, the present disclosure thus provides methods that involve such comparison.

Exemplification

Example 1: Materials and Methods

Data Analysis

[0217] All analyses, unless otherwise stated, were done on RStudio Version 1.2 utilizing R version 3.6 (*See*, RStudio Team, "Rstudio: Integrated Development for R", 2019; *see also*, R Core Team, R: "A language and environment for statistical computing", 2020).

Algorithm development

[0218] Elastic net regularized linear net models can be employed to create individual subclassifying models for BL1, BL2, LAR, MSL, M, and IM subtypes with each independent subtype treated as a multinomial variable. Genes utilized for the M and IM subtype classifications within this model can then be used to derive a logistic elastic net model on the new data set, removing genes whose probes are reassigned between analyses. Strength of association with classification variables can then be assessed using ten-fold cross validation of misclassification error. Model threshold for determining immuno-oncology (IO) score can be determined using maximum area under the curve (AUC). In some embodiments, model threshold for determining immuno-oncology (IO) score may be adjusted for particular patients and/or tumor samples. For example, in some embodiments, model threshold may be increased for patients with tumors that are particularly agressive (*e.g.*, requiring high level of treatment efficacy within a shortened time period). In some embodiments, model threshold may be decresased if one or more therapies of interest (*e.g.*, ICI therapy) has low toxicity when administered to a subject and/or subject tissue. In some embodiments, model threshold may be adjusted to account for one or more therapies already administered and/or currently being administered to a subject. In some embodiments, model threshold may be adjusted to account for one or more additional therapies (*e.g.*, non-ICI therapies) already administered and/or currently being administered to a subject. For example, in some embodiments, model threshold may be adjusted to account for one or

more additional non-ICI therapies already administered and/or currently being administered prior to an ICI therapy.

Gene expression dataset processing

[0219] Twenty-five gene expression profile data sets, representing three microarray platforms, were downloaded from the publicly available Gene Expression Omnibus (GEO, ncbi.nlm.nih.gov/geo/). Data were combined from raw microarray expression (CEL) files collectively normalized by robust multiarray average (RMA), and log transformed. Samples from this data set were pared down to triple negative status using a bimodal distribution of ESR1, ERBB2, and PGR genes, resulting in 1284 unique TNBC samples. Of these, 994 unique TNBC samples were used to train the model, and the remaining 335 unique TNBC samples were used for model validation.

[0220] For genes represented by multiple probes, the probe with the highest inter-quartile range was selected to prioritize genes with a large dynamic range of expression. Batch correction was performed using an Empirical Bayes method, ComBat (*See,* Johnson *et al.*, "Adjusting batch effects in microarray expression data using empirical Bayes methods", *Biostatistics*, 8, 2007, incorporated herein by reference in its entirety). Patient datasets were previously made publicly available under the ethical policies of the National Institutes of Health's Gene Expression Omnibus (GMO) database. No additional ethics review was required for the in-silico analysis of these datasets.

[0221] Table 12: Source of TNBC specimens for Training and Validation

Dataset	TNBC Specimens	Dataset	TNBC Specimens
GSE1456	44	GSE7904	17
GSE1561	21	GSE10780	5
GSE2034	59	GSE11121	21
GSE2109	55	GSE12093	57
GSE2603	35	GSE12763	5
GSE2990	11	GSE13787	10
GSE3494	27	GSE16716	62
GSE3744	17	GSE25066	178
GSE5327	35	GSE31519	67
GSE5364	36	GSE58812	107
GSE5462	2	GSE76124	198
GSE6596	8	GSE76250	165
GSE7390	42		

Model building

[0222] Model building for the 27-gene immuno-oncology algorithm was performed using R version 3.5.2 (Figure 6). The 101-gene signature was used to identify gene sets that distinguished the classes via gene set enrichment analysis (GSEA) using the C2 curated gene sets of canonical pathways (*See,* Subramanian *et al.*, "Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles", *PNAS*, 102, 2005, incorporated herein by reference in its entirety). Elastic-net regularized linear models were employed to create individual subclassifying models for the BL1, BL2, LAR, MSL, M, and IM subtypes with the subtypes treated as a multinomial variable (*See*, Friedman *et al.*, "Regularization Paths for Generalized Linear Models via Coordinate Descent", *J Stat Softw*, 33, 2010, incorporated herein by reference in its entirety). The 30 genes utilized for the M and IM subtype classifications with this model were then used to derive a logistic elastic net model on the new data set, minus three genes whose probes had been reassigned between analyses. Strength of association with classification variables was assessed using ten-fold cross validation of the misclassification error. The model threshold for determining the immuno-oncology score (IO score) was determined using the maximum area under the curve (AUC) (*See*, Hajian-Tilaki *et al.*, "Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation", 4, 2013, each of which is incorporated herein by reference in its entirety), in contrast to the significance of the correlation method for determining threshold previously described by Ring et al..

GSE81838 dataset analysis of TNBC tumor epithelial and adjacent stromal tissue

[0223] Microarray data was obtained from GSE81838 where laser-capture microdissection had been performed on 10 TNBC tumors to isolate malignant epithelial cell-enriched areas and the adjacent stromal cell-containing areas of the tumor sections (*See*, Lehmann *et al.* "Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection ", 11, June 2016, incorporated herein by reference). The IO scores for each sample were obtained and correlated between the matched tumor epithelial and adjacent stromal tissue using Spearman's method.

TCGA breast cancer datasets and analysis

[0224] Gene expression profiles from breast cancer specimens collected for The Cancer Genome Atlas (TCGA) were obtained from the National Cancer Institute Genomic Data Commons Data Portal. TNBC status was confirmed by bimodal modeling of ESR1, PGR, and ERBB2 gene expression, resulting in 180 total samples with matching tumor

infiltrating lymphocytes (TILs) presence and intensity as described in Lehmann *et al* . Neutrophil presence was obtained by the TCGA study investigators and aligned to the TNBC samples. The IO scores of samples with intense TIL staining and samples with neutrophil presence of 30% or greater was assessed by the Welch t-test for significance.

GEO non-small cell lung cancer (NSCLC) datasets and analysis

[0225] The clinical response to immunomodulation therapy and expression data of NSCLC patients in the GSE135222 (27 patients) and GSE126044 (16 patients) cohorts was obtained from GEO. Response was measured in both cohorts using Response Evaluation Criteria in Solid Tumors (RESCIST) metrics, where patients exhibiting partial response or stable disease for >6 months were classified as responders (*See*, Schwartz *et al.*, "RECIST 1.1-Update and clarification: From the RECIST committee", *Eur J Cancer*, 62, 2016; *see also*, Jung *et al.*, "DNA methylation loss promotes immune evasion of tumours with high mutation and copy number load", *Nat Commun*, 10, 2019; *see also*, Kim *et al.*, "Single-cell transcriptome analysis reveals TOX as a promoting factor for T cell exhaustion and a predictor for anti-PD-1 responses in human cancer", *Genome Med*, 12, 2020; each of which is incorporated herein by reference in its entirety). Because response was defined in the same manner for both cohorts, we were able to combine the data for purposes of the analysis. Expression data from the combined cohort were processed using the 27-gene algorithm and analyzed by IO score. The difference in IO score between responders and non-responders was evaluated for significance using the Welch t-test. The data from the combined cohort was then evaluated for the correlation of IO score to objective response. The predefined threshold was used to divide patients into IO score positive and negative and compared to objective response to calculate an odds ratio.

Example 2: Distinguishing quiescent from active tumor microenvironment

[0226] The present Example describes technologies for distinguishing quiescent from active tumor microenvironments through assessment of certain gene expression patterns or characteristics. In particular, the present Example describes determination of an IO score for a particular tumor sample, as reflective of the quiescent or immunologically active state of the TME. As described herein, without wishing to be bound by any particular theory, we propose that a negative IO score may indicate a quiescent state, where the tumor cells are more actively promoting angiogenesis, inducing an inflammatory response, and stimulating cancer-associated fibroblasts which collectively is constructing extracellular

matrix. By comparison, a positive IO score may indicate one or more of: 1) a tumor poised to transition to an immunologically active TME (e.g. upon administration of an ICI); and 2) an immunologically active TME with reduced inflammatory characteristics combined with an increase in the innate and adaptive immune systems increasing tumor cell invasion. Further, using the IO score as a continuous variable may be predictive to the intensity and durability of response and correlate with clinical efficacy (*e.g*, objective response). Whereas a biomarker, e.g. an immune checkpoint receptor such as PD-L1, may be present in both states, the present disclosure describes development of small gene set(s) – such as the 27-gene algorithm described herein - able to distinguish a quiescent from an active TME.

Example 3: Concordance between IO Score and IM status

[0227] The present Example confirms that IO scores determined using the 27-gene immuno-oncology algorithm correlate with IM scoring statuses from a previous 101-gene model. An independent expression-based centroid model, defined by M and IM features of a previous 101-gene model, were obtained through elastic net modeling to produce a total of 27 genes. These 27 genes were combined in an independent algorithm to generate IO scores corresponding to likelihood of response to immunomodulation therapy. The 27-gene immuno-oncology algorithm was compared to the previous 101-gene model through validation of 335 unique TNBC samples, resulting in 88% concordance for IO+/IM+ and IO-/IM- scores, as shown in Table 13 below.

[0228] Table 13: Concordance between IM status from the 101-gene model and IO score from the 27-gene immuno-oncology algorithm within the validation cohort of 335 unique TNBC samples.

		101-gene	
		IM+	IM-
27-gene	IO+	82 (24%)	37 (11%)
	IO-	2 (1%)	214 (64%)

Example 4: Correlation of IO Score to tumor epithelial and adjacent stromal tissue in TNBC

[0229] The present Example demonstrates that IO scores determined in accordance with the present disclosure can serve as a measure of the tumor microenvironment (TME) spanning tumor and stromal regions.

[0230] IO Scores were calculated for matched TNBC tumor epithelial and adjacent stromal tissue samples in the GSE81838 dataset. Due to low sample size (20 samples from 10 patients), IO scores for matched tumor epithelial and adjacent stromal tissue samples were calculated using Spearman's method. Correlation of IO scores between tissue types was calculated to be 92.7% ($p<0.001$) when matched to each patient, suggesting that IO score is a measure of TME spanning at least tumor and stromal regions.

Example 5: IO Scoring of TNBC samples with TILs or neutrophils

[0231] The present Example demonstrates that IO scores determined in accordance with the present disclosure can correlate with levels of tumor infiltrating lymphocytes (TILs) and neutrophils. High levels of TILs may indicate an active immunological state and improved outcome after immunomodulation therapy, while increased levels of neutrophils may correspond to a quiescent immunological state and reduced response to immunomodulation therapy. IO Scores were evaluated for samples obtained from The Cancer Genome Atlas (TCGA), including triple negative breast cancer (TNBC) samples with high TILs and samples with increased neutrophil load. A statistically significant (Figure 2, $p=0.0092$) difference in IO score was seen between TNBC samples with high TILs (IO Score = 0.09) and samples with increased neutrophil load (IO Score = -0.30), indicating that a positive IO Score may possess features associated with a positive outcome after immunomodulation therapy while a negative IO Score may indicate poor immunomodulation therapy response.

Example 6: Correlation of IO Score to immunomodulation therapy response in NSCLC patients

[0232] The present Example demonstrates that IO scores determined in accordance with the present disclosure can indicate potential response to immunomodulation therapy. IO Scores were evaluated for a combined cohort of non-small cell lung cancer (NSCLC) patients, where response to immunomodulation therapy was defined as exhibiting partial response or stable disease for at least 6 months. Average IO score for responders (IO Score

= 0.29) and non-responders (IO Score = -0.096) was found to be significantly by the Welch t-test (Figure 3, p=0.0035).

Example 7: Correlation of Mesenchymal Score to focal adhesion kinase (FAK) inhibitor sensitivity in NSCLC xenografts.

[0233] The present Example demonstrates that using the 27-gene immuno-oncology algorithm described herein it is possible to predict sensitivity to FAK inhibitor drugs which may subsequently be used for immunomodulation of the TME. Adenocarcinoma xenograft model data were attained from GSE109302 and assessed by the 27-gene immuno-oncology algorithm. Of the 10 NSCLC cell lines, five were resistant and five were sensitive to the drug BI 853520. The average mesenchymal score for the resistant group was 0.076 and the sensitive group was 0.358 (p=0.025). Without wishing to be bound by any particular theory, these data demonstrate it may be possible to identify patients who will benefit from drugs which act upon the TME to improve immunomodulation (e.g., by pushing a "poised" tumor into a "hot" state as described herein), either alone or in combination with ICIs.

Example 8A: Exemplary gene sets

[0234] In some embodiments, a gene set for use in accordance with the present disclosure comprises at least one gene from the following group:

[0235] Group A: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1.

[0236] In some embodiments, such a gene set may include all genes from Group A.

Example 8B: Exemplary gene sets

[0237] In some embodiments, a gene set for use in accordance with the present disclosure includes at least one gene from each of the following groups:

[0238] Group B1: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10;

[0239] Group B2: COL2A1, FOXC1, KRT16, MIA, SFRP1;

[0240] Group B3: APOD, ASPN, HTRA1;

[0241] In some embodiments, such a gene set may include at least one gene from each of Group B1 and Group B2, and more than one gene from Group B3. In some embodiments, such a gene set may include at least one gene from each of Group B2 and Group B3, and more than one gene from Group B1. In some embodiments, such a gene set may include at least one gene from each of Group B1 and Group B3, and more than one gene from Group B2.

Example 8C: Exemplary gene sets

[0242] In some embodiments, a gene set for use in accordance with the present disclosure includes at least one gene from each of the following groups:

[0243] Group C1: SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5;

[0244] Group C2: TNFAIP8, TNFSF10;

[0245] Group C3: RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG;

[0246] Group C4: CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273;

[0247] Group C5: CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6;

[0248] Group C6: KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2;

[0249] Group C7: APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1;

[0250] Group C8: ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16;

[0251] Group C9: GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3;

[0252] Group C10: HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R;

[0253] Group C11: BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1;

[0254] Group C12: C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3;

[0255] Group C13: FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1;

[0256] Group C14: ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12;

[0257] Group C15: MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2;

[0258] Group C16: ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1;

[0259] Group C17: TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1;

[0260] Group C18: ITGBL1, ASPN, PDGFRB, HTRA1, HEG1;

[0261] Group C19: ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1;

[0262] Group C20: TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19.

[0263] In some embodiments, such a gene set may include at least one gene from each of Group C3, Group C4, Group C5, Group C7, Group C9, Group C10, Group C11, Group C12, Group C13, Group C14, Group C15, Group C16, Group C17, and Group C20 and more than one gene from Group C1, Group C2, Group C6, Group C8, Group C18, and Group C19.

Example 8D: Exemplary gene sets

[0264] In some embodiments, a gene set for use in accordance with the present disclosure includes at least one gene from the following group:

[0265] Group D1: ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33,

INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24.

[0266] In some embodiments, a gene set for use in accordance with the present disclosure includes fewer than all of the genes in Group D1; in some such embodiments, a gene set for use in accordance with the present disclosure includes fewer than or equal to 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 29, 28, 27 or fewer genes from Group D1.

[0267] In some embodiments, a gene set according to any one of Examples 8A-C includes one or more genes from Group D1.

Example 9: IO Scoring of Bladder Cancer samples

[0268] The present Example confirms that IO scores determined in accordance with the present disclosure can indicate potential response to immunomodulation therapy for various tumor types, including *e.g.*, bladder cancer.

[0269] Gene expression data for 1188 breast cancer samples were downloaded and compared against an established molecular classifier (Ring *et al.* 2016), which selected the top 3000 genes correlated with IM, MSL, and M signatures for TNBC. The 3000 gene set was generated through assessment of the Ring *et al.* IM, MSL, M signatures (previously identified in TNBC) for two additional tumor types (lung adenocarcinoma and lung squamous cell carcinoma). The gene lists from all three gene expression datasets were compared and 939 genes were selected as being classifiers for IM, MSL, M based on their presence in all three gene lists. Gene expression data for 406 bladder cancer patients were downloaded and assessed using the 27-gene immuno-oncology algorithm described herein. Expression of these 939 genes were then plotted in a heatmap, clustered by signature type and patient group (Figure 8). The 27-gene immuno-oncology algorithm IO binary score was overlaid on the heatmap, displaying an association with an IM, immunologically "hot" classification (Figure 9, Figure 10). These data confirm that a positive score result from the

27-gene immuno-oncology algorithm does associate with genes known to have a high, potentially active, immune function.

[0270] Furthermore, hierarchical gene clustering confirms that variations of the particular 27-gene set (*e.g.*, including one or more changes represented in exemplary gene sets provided herein) are useful as described herein, including specifically in assessments of bladder cancer.

[0271] Hierarchical clustering of the resulting gene expression data (*See*, Ward, 1963, which is incorporated herein by reference in its entirety) was used to identify genes that clustered together, or metagenes, within these heatmaps. In particular, metagenes containing one or more of the 27 genes assessed as part of the immuno-oncology algorithm were evaluated. Within this subset of thirteen metagenes, a total of 198 genes were identified that could potentially be selected as alternative genes for use in the 27-gene immuno-oncology algorithm. Additionally, gene set enrichment analysis (*See*, Subramanian 2005, incorporated herein by reference in its entirety) of metagenes identified certain associated cellular pathways that might be of interest for assessment of tumor samples (Figure 10). In some embodiments, these pathways may be associated with one or more genes from the 27 gene set associated with the 27-gene immuno-oncology algorithm disclosed herein (*e.g.*, one or more of the 27 genes or their gene products may participate in the pathways). Alternatively or additionally, in some embodiments, these pathways may be associated with a specific IO score (*e.g.*, a positive or negative score). Thus, teachings provided herein may permit selection of alternative gene sets to the 27 gene set explicitly described herein, for example including a reasonably comparable number of genes (*e.g.*, about 10 to about 20, about 20 to about 30, about 30 to about 40, about 40 to about 50, etc.), that achieve useful tumor classification (*e.g.*, define an IO score that discriminates) as described herein. In some embodiments, such sets may include one or more of the 27 genes of the exemplified 27 gene set, optionally in combination with one or more genes that participate in these pathways, which may be the same as or different from other genes in the exemplified 27 gene set.

[0272] Among other things, experiments confirmed that the 27-gene immuno-oncology algorithm scoring threshold, which is used as a cutoff for designating a tumor score as "positive" or "negative", was sufficiently accurate for use in other tumor types, *e.g.*, bladder cancer (Figure 11). A new threshold was calculated based upon the intersection of

sensitivity and specificity within bladder patient data (Habibzadeh 2016, incorporated herein by reference in its entirety) and found to have identical accuracy as compared to a previously established threshold. Therefore the original threshold was maintained for IO scoring. Thus, the present disclosure confirms, among other things, that the 27 gene set defines useful IO thresholds in a variety of cancers and, furthermore that such thresholds provide comparable accuracy, and/or are otherwise reasonably comparable (e.g., are within a range of about 0.1 +/- 0.02).

[0273] The 27-gene immuno-oncology algorithm of the present disclosure was also applied to data for a clinical cohort of bladder cancer patients treated with an immune checkpoint inhibitor (atezolizumab) in the IMVigor210 trial. Among other things, it was determined that the 27-gene immuno-oncology algorithm was able to provide a prediction of overall survival rates within the trial, based upon corresponding IO scores (Figure 12).

Example 10: IO Scoring of Renal Cancer samples

[0274] The present Example confirms that IO scores determined in accordance with the present disclosure can indicate potential response to immunomodulation therapy for various tumor types, including, *e.g.*, renal cancer.

[0275] Gene expression data for 403 clear cell kidney cancer and 203 papilloma kidney cancer patients were assessed using the 27-gene immuno-oncology algorithm described herein. Result IO scores were plotted against the 939 genes described in Example 9 above to produce heatmaps, which were clustered by signature type (IM, M, MSL) and patient group. These data confirm that a positive score result from the 27-gene immuno-oncology algorithm does associate with genes known to have a high, potentially active, immune function in certain kidney cancers.

[0276] Further experiments analyzed RNAseq data from a group of 43 renal cell carcinoma (RCC) patients that had been treated with an immuno-oncology therapy and monitored for one-year progression free survival (PFS). Patient data was assessed using the 27-gene immuno-oncology algorithm and it was found that patients with a positive IO score had significantly better one-year PFS compared to those with a negative IO score. These results confirm that the 27-gene immuno-oncology algorithm of the present disclosure has a strong correlation with response to ICI therapy in renal cancer and further support applicability of the algorithm in multiple cancer types.

Example 11: Assessment of data from alternative biological vectors

[0277] The present Example, among other things, demonstrates that classifications provided herein can be correlated with data from alternative biological vectors (e.g., data re miRNA expression, methylation status, protein expression level, protein modification status, etc.) so that, in various embodiments, one or more different types of biological data may be utilized for and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0278] For example, as described herein, for a given set of patient samples for which gene expression data is obtained and IM, MSL and M centroids are assessed as described herein, matched data sets are collected along one or more alternative biological vector(s). These matched data sets can then be mapped to the gene expression centroids, which act as a reference to reveal components indicative or reflective of IM, MSL, and M features. In some embodiments, information obtained from matched data sets can be used to inform selection of one or more therapies (e.g., ICI therapy). In some embodiments, information obtained from matched data sets can be used to inform selection of combination therapies (e.g., additional therapy in combination with ICI therapy). In some embodiments, information obtained from matched data sets can be used to inform selection of one or more alternative therapies (e.g., a therapy other than ICI therapy). Thus, the present disclosure demonstrates that miRNA expression, rather than or in addition to, gene expression patterns of selected gene sets as described here, can be utilized to select and/or monitor patients for responsiveness to therapies and/or for particular characteristics of or changes in immune status.

Example 12: Assessment of data from miRNA targeting exemplary gene sets

[0279] The present Example, among other things, demonstrates that classifications provided herein can be correlated with pre-miRNA expression data and may be utilized for and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0280] A list of pre-miRNAs targeting at least one gene within the 101-gene signature was generated using a miRNA target prediction database, miRDB (http://mirdb.org/). These pre-miRNAs were then independently mapped to the IM, M, and MSL centroids (*e.g.*, a pre-miRNA mapping to the IM centroid would be classified as

having an IM signature). Classified pre-miRNAs were then assessed to determine, for example, whether an pre-miRNA was classified under a different signature than one or more of its corresponding target genes.

[0281] In some embodiments, a tumor sample (*e.g.*, obtained through liquid biopsy, tissue biopsy, etc.) may be assessed to determine expression level of one or more classified pre-miRNAs as described herein. In some embodiments, treatments targeting or inhibiting miRNAs (*e.g.*, pre-miRNAs, mature miRNAs, combinations thereof) classified under a different subtype as compared to one or more target genes could produce a shift in mRNA levels for said one or more target genes, resulting in changes in tumor signatures and/or IO scoring. For example, in some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) classified as one subtype (*e.g.*, M, MSL) targeting a gene classified as a different subtype (*e.g.*, IM) could produce an increase in overall IM signature for a tumor and result in an increased IO score. In some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) classified as one subtype(*e.g.*, IM) targeting a gene classified as a different subtype (*e.g.*, M, MSL) could produce an increase in overall M or MSL signature for a tumor and result in a decreased IO score. In some embodiments, information obtained from miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) assessment can be used to inform treatment decisions – e.g., selection and/or modification of therapy. In some particular embodiments, information obtained from miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) assessment can be used to inform selection and/or modification of combination therapies (e.g., additional therapy in combination with ICI therapy). In some embodiments, information obtained from matched data sets can be used to inform selection and/or modification of therapies, and in particular of combination therapies (e.g., additional therapy in combination with ICI therapy) based upon changes in IO scoring. In some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) could be combined with one or more therapies (*e.g.*, chemotherapy, ICI, etc.) based upon changes in IO scoring.

Example 13: Development of scoring method based upon miRNA expression

[0282] The present Example, among other things, demonstrates that methods and technologies described herein may be adapted for development of a immuno-oncology

algorithm to measure miRNA levels in the TME and generate an associated score predicting or otherwise characterizing response to immunomodulation therapy treatment.

[0283] Gene and pre-miRNA expression datasets for eight cancers were downloaded from the genomic data commons (GDC) portal (https://portal.gdc.cancer.gov/) using the Genomic Data Commons package in R. Assessed cancers included Bladder Urothelial Carcinoma (BLCA), Breast invasive carcinoma (BRCA), Colon Adenocarcinoma (COAD), Lung Adenocarcinoma (LUAD), Lung squamous cell carcinoma (LUSC), Ovarian serous cystadenocarcinoma (OV), Stomach adenocarcinoma (STAD) and Head and Neck squamous cell carcinoma (HNSC). Subtype (IM, M, MSL) was calculated as previously described for each sample in the datasets. STAD (n=407) and HNSC (n=545) were categorized as true test sets and OV (n=397) was used as a validation cohort. Remaining cancer datasets (BLCA, BRCA, COAD, LUAD and LUSC) were then split, with 5% of each dataset reserved to create a small validation set (n=137) and 95% concatenated to create the training set (n=2557).

[0284] With the training set established, calculations were performed to generate the spearman rho correlation coefficient between expression of pre-miRNA across all samples and subtype (IM, M, MSL), yielding three spearman rho values. Spearman rho values with a p value of $<.05$ were removed from the set. Three lists of pre-miRNAs were generated containing 75 pre-miRNAs with the highest spearman rho values in a corresponding subtype (*e.g.*, 75 pre-miRNAs for each of IM, M, and MSL). A total of 179 unique pre-miRNAs (Table 14) were obtained from this assessment, with 46 miRNAs overlapping between lists for M and MSL. Intersection of all three phenotypes was considered an empty set.

[0285] Table 14: Selected pre-miRNAs with highest spearman rho coefficient in IM, M, and MSL types.

miRNA		
hsa-mir-6720	hsa-mir-5586	hsa-mir-101-1
hsa-let-7g	hsa-mir-30a	hsa-mir-655
hsa-mir-4491	hsa-mir-616	hsa-mir-483
hsa-mir-146b	hsa-mir-222	hsa-mir-100
hsa-mir-3682	hsa-mir-18a	hsa-mir-19a
hsa-mir-223	hsa-mir-495	hsa-mir-488
hsa-mir-490	hsa-mir-29b-2	hsa-mir-146a
hsa-mir-7-3	hsa-mir-27b	hsa-mir-378c
hsa-mir-148a	hsa-mir-942	hsa-mir-16-2

hsa-mir-3926-2	hsa-let-7a-1	hsa-mir-181c
hsa-mir-502	hsa-mir-4453	hsa-mir-4780
hsa-mir-202	hsa-mir-576	hsa-mir-4740
hsa-mir-6507	hsa-mir-1296	hsa-mir-7-2
hsa-mir-485	hsa-mir-30e	hsa-mir-5694
hsa-mir-29c	hsa-mir-199a-2	hsa-mir-497
hsa-mir-4772	hsa-mir-6891	hsa-mir-1301
hsa-mir-32	hsa-mir-505	hsa-mir-433
hsa-mir-625	hsa-mir-579	hsa-mir-139
hsa-mir-590	hsa-mir-7702	hsa-mir-3677
hsa-mir-494	hsa-mir-3194	hsa-mir-379
hsa-let-7c	hsa-mir-5002	hsa-mir-3150b
hsa-mir-10a	hsa-mir-577	hsa-mir-101-2
hsa-mir-127	hsa-mir-1247	hsa-mir-432
hsa-mir-147b	hsa-mir-125b-1	hsa-mir-186
hsa-mir-143	hsa-mir-381	hsa-mir-501
hsa-mir-3940	hsa-let-7a-3	hsa-mir-218-1
hsa-mir-409	hsa-mir-3136	hsa-mir-4524a
hsa-mir-4736	hsa-mir-376c	hsa-mir-766
hsa-mir-496	hsa-mir-133b	hsa-mir-301a
hsa-mir-340	hsa-mir-3926-1	hsa-mir-493
hsa-mir-382	hsa-mir-643	hsa-let-7b
hsa-mir-585	hsa-mir-150	hsa-mir-3922
hsa-mir-299	hsa-mir-133a-1	hsa-mir-5571
hsa-mir-181d	hsa-mir-7-1	hsa-mir-3074
hsa-mir-377	hsa-mir-511	hsa-mir-6788
hsa-mir-380	hsa-mir-214	hsa-mir-129-2
hsa-mir-218-2	hsa-mir-758	hsa-mir-129-1
hsa-mir-376a-1	hsa-mir-199a-1	hsa-mir-3690-1
hsa-mir-1258	hsa-mir-28	hsa-mir-7846
hsa-mir-454	hsa-mir-431	hsa-let-7a-2
hsa-mir-1-1	hsa-mir-337	hsa-mir-665
hsa-mir-889	hsa-mir-5690	hsa-mir-140
hsa-mir-195	hsa-mir-142	hsa-mir-29b-1
hsa-mir-216a	hsa-mir-370	hsa-mir-15b
hsa-mir-16-1	hsa-mir-204	hsa-mir-383
hsa-mir-5683	hsa-mir-5685	hsa-mir-145
hsa-mir-369	hsa-mir-329-1	hsa-mir-541
hsa-mir-192	hsa-mir-4434	hsa-mir-342
hsa-let-7e	hsa-mir-155	hsa-let-7i
hsa-mir-548s	hsa-mir-10b	hsa-mir-487a
hsa-mir-3613	hsa-mir-411	hsa-mir-4999
hsa-mir-605	hsa-mir-3622a	hsa-mir-133a-2
hsa-mir-135a-2	hsa-mir-3614	hsa-mir-23b
hsa-mir-199b	hsa-mir-5691	hsa-mir-410

hsa-mir-148b	hsa-mir-487b	hsa-mir-6718
hsa-mir-6510	hsa-mir-29a	hsa-mir-217
hsa-mir-656	hsa-mir-628	hsa-mir-99a
hsa-mir-134	hsa-mir-1-2	hsa-mir-654
hsa-mir-4677	hsa-mir-215	hsa-mir-6716
hsa-mir-125b-2	hsa-mir-330	

[0286] Interquartile range (IQR) for expression was assessed for each of these 179 pre-miRNAs to determine which pre-miRNAs had a robust range of expression values. Pre-miRNAs with an IQR greater than 1 were selected for additional analysis, resulting in130 unique pre-miRNAs total, which are outlined in Table 15.

[0287] Next, selected pre-miRNAs were evaluated for presence of corresponding mature miRNA in real-world plasma samples. Data from GSE73002 of the NCBI gene expression omnibus (https://www.ncbi.nlm.nih.gov/geo/) were downloaded and this dataset (containing serum miRNA expression levels for breast cancer detection) was assessed for presence of selected mature miRNAs. A total of 119 unique pre-miRNAs were identified in the dataset.

[0288] Table 15: Selected pre-miRNAs with IQR>1.

miRNA		
hsa-mir-6720	hsa-mir-5586	hsa-mir-146a
hsa-mir-146b	hsa-mir-30a	hsa-mir-378c
hsa-mir-223	hsa-mir-616	hsa-mir-16-2
hsa-mir-7-3	hsa-mir-222	hsa-mir-181c
hsa-mir-148a	hsa-mir-18a	hsa-mir-7-2
hsa-mir-502	hsa-mir-495	hsa-mir-497
hsa-mir-485	hsa-mir-29b-2	hsa-mir-1301
hsa-mir-29c	hsa-mir-27b	hsa-mir-139
hsa-mir-4772	hsa-mir-942	hsa-mir-3677
hsa-mir-32	hsa-mir-576	hsa-mir-379
hsa-mir-625	hsa-mir-1296	hsa-mir-3150b
hsa-mir-590	hsa-mir-199a-2	hsa-mir-101-2
hsa-mir-494	hsa-mir-505	hsa-mir-432
hsa-let-7c	hsa-mir-7702	hsa-mir-501
hsa-mir-10a	hsa-mir-577	hsa-mir-218-1
hsa-mir-127	hsa-mir-1247	hsa-mir-766
hsa-mir-147b	hsa-mir-125b-1	hsa-mir-301a
hsa-mir-143	hsa-mir-381	hsa-mir-493
hsa-mir-3940	hsa-mir-376c	hsa-let-7b
hsa-mir-409	hsa-mir-133b	hsa-mir-3074
hsa-mir-496	hsa-mir-150	hsa-mir-129-2

hsa-mir-340	hsa-mir-133a-1	hsa-mir-129-1
hsa-mir-382	hsa-mir-7-1	hsa-mir-3690-1
hsa-mir-299	hsa-mir-511	hsa-mir-140
hsa-mir-181d	hsa-mir-214	hsa-mir-29b-1
hsa-mir-377	hsa-mir-758	hsa-mir-15b
hsa-mir-380	hsa-mir-199a-1	hsa-mir-145
hsa-mir-218-2	hsa-mir-431	hsa-mir-342
hsa-mir-1258	hsa-mir-337	hsa-mir-4999
hsa-mir-454	hsa-mir-142	hsa-mir-133a-2
hsa-mir-1-1	hsa-mir-370	hsa-mir-23b
hsa-mir-889	hsa-mir-204	hsa-mir-410
hsa-mir-195	hsa-mir-155	hsa-mir-6718
hsa-mir-16-1	hsa-mir-10b	hsa-mir-217
hsa-mir-5683	hsa-mir-411	hsa-mir-99a
hsa-mir-369	hsa-mir-3614	hsa-mir-654
hsa-mir-192	hsa-mir-487b	
hsa-let-7e	hsa-mir-29a	
hsa-mir-3613	hsa-mir-628	
hsa-mir-135a-2	hsa-mir-1-2	
hsa-mir-199b	hsa-mir-215	
hsa-mir-148b	hsa-mir-330	
hsa-mir-6510	hsa-mir-101-1	
hsa-mir-656	hsa-mir-655	
hsa-mir-134	hsa-mir-483	
hsa-mir-4677	hsa-mir-100	
hsa-mir-125b-2	hsa-mir-19a	

[0289] Next, pre-miRNA interactions with potential target genes were mapped through use of miRDB (http://mirdb.org/), a miRNA target prediction database. A total of 113 pre-miRNAs were identified as potentially having at least one gene target in the 101-gene signature listing (Table 16) and 73 pre-miRNAs were identified as potentially having at least one gene target in the DetermaIO gene set (Table 17). These pre-miRNAs were also assigned a probability of interaction with each gene. Further analysis produced a list of pre-miRNAs with a target in either the 101 gene signature (Table 18) or the DetermaIO gene set (Table 19) having a probability of at least 70%.

[0290] Table 16: pre-miRNAs with predicted target in 101 gene signature list.

pre-miRNA		
hsa-mir-379	hsa-mir-18a	hsa-mir-140
hsa-let-7c	hsa-mir-15b	hsa-mir-340
hsa-mir-889	hsa-mir-628	hsa-mir-576
hsa-mir-493	hsa-mir-7702	hsa-mir-501

hsa-mir-758	hsa-mir-625	hsa-mir-377
hsa-let-7e	hsa-mir-218-2	hsa-mir-299
hsa-mir-29b-2	hsa-mir-3940	hsa-mir-27b
hsa-mir-4999	hsa-mir-139	hsa-mir-16-1
hsa-mir-766	hsa-mir-410	hsa-mir-616
hsa-mir-155	hsa-mir-148a	hsa-mir-655
hsa-mir-942	hsa-mir-378c	hsa-mir-497
hsa-mir-5683	hsa-mir-129-1	hsa-mir-494
hsa-mir-29a	hsa-mir-3613	hsa-mir-495
hsa-mir-431	hsa-mir-150	hsa-mir-142
hsa-mir-656	hsa-mir-125b-2	hsa-mir-1301
hsa-mir-3614	hsa-mir-370	hsa-mir-6510
hsa-mir-4677	hsa-mir-10b	hsa-mir-204
hsa-mir-143	hsa-mir-145	hsa-mir-369
hsa-mir-337	hsa-mir-502	hsa-mir-3677
hsa-mir-3074	hsa-mir-133b	hsa-mir-496
hsa-mir-100	hsa-mir-4772	hsa-mir-218-1
hsa-mir-214	hsa-mir-195	hsa-mir-222
hsa-mir-215	hsa-mir-199b	hsa-mir-5586
hsa-mir-181d	hsa-mir-483	hsa-mir-382
hsa-mir-134	hsa-mir-454	hsa-mir-148b
hsa-mir-511	hsa-mir-147b	hsa-mir-192
hsa-mir-146a	hsa-mir-381	hsa-mir-577
hsa-mir-217	hsa-mir-485	hsa-mir-127
hsa-mir-181c	hsa-mir-146b	hsa-mir-19a
hsa-mir-3150b	hsa-mir-29c	hsa-mir-10a
hsa-mir-411	hsa-mir-7-1	hsa-mir-342
hsa-mir-16-2	hsa-mir-301a	hsa-mir-590
hsa-mir-654	hsa-mir-129-2	hsa-mir-432
hsa-mir-380	hsa-mir-1296	hsa-mir-32
hsa-mir-409	hsa-let-7b	hsa-mir-223
hsa-mir-30a	hsa-mir-505	hsa-mir-330
hsa-mir-23b	hsa-mir-487b	hsa-mir-6720

[0291] Table 17: pre-miRNAs with predicted target in DetermaIO gene list.

miRNA	Gene Accession Number	Probability of Targeting	Gene Name
hsa-mir-146b	NM_001278736	81.6941	CCL5
hsa-mir-223	NM_004863	81.1901	SPTLC2

hsa-mir-148a	NM_001844	73.4678	COL2A1
hsa-mir-485	NM_001171581	83.1959	ITM2A
hsa-mir-29c	NM_001844	97.45356	COL2A1
hsa-mir-4772	NM_002775	78.3221	HTRA1
hsa-mir-4772	NM_004863	56.5861	SPTLC2
hsa-mir-32	NM_001453	56.3943	FOXC1
hsa-mir-32	NM_004863	58.89778	SPTLC2
hsa-mir-32	NM_003012	54.10264	SFRP1
hsa-mir-32	NM_004419	91.93814	DUSP5
hsa-mir-32	NM_001193335	84.3651	ASPN
hsa-mir-625	NM_003012	50.5249	SFRP1
hsa-mir-590	NM_004863	58.70663	SPTLC2
hsa-mir-590	NM_001302123	58.31867	CXCL11
hsa-mir-494	NM_001190943	65.46408	TNFSF10
hsa-let-7c	NM_001171581	89.4822	ITM2A
hsa-mir-496	NM_001171581	53.6328	ITM2A
hsa-mir-340	NM_001190943	56.8947	TNFSF10
hsa-mir-299	NM_001077654	93.57209	TNFAIP8
hsa-mir-181d	NM_004419	70.5801	DUSP5
hsa-mir-181d	NM_001193335	73.0576	ASPN
hsa-mir-181d	NM_001190943	51.8133	TNFSF10
hsa-mir-181d	NM_001193335	85.7785	ASPN
hsa-mir-380	NM_001453	84.3932	FOXC1
hsa-mir-889	NM_001844	95.91891	COL2A1
hsa-mir-16-1	NM_004419	74.7026	DUSP5
hsa-mir-16-1	NM_003012	72.3666	SFRP1
hsa-mir-5683	NM_002164	58.29101	IDO1
hsa-mir-369	NM_001193335	51.33138	ASPN
hsa-mir-192	NM_003012	54.4194	SFRP1
hsa-mir-192	NM_001193335	77.7057	ASPN
hsa-mir-3613	NM_004419	87.96533	DUSP5
hsa-mir-3613	NM_001171581	68.55283	ITM2A
hsa-mir-3613	NM_001171581	81.5659	ITM2A
hsa-mir-199b	NM_001302123	58.422	CXCL11
hsa-mir-199b	NM_004419	55.1577	DUSP5
hsa-mir-199b	NM_004863	50.36683	SPTLC2
hsa-mir-148b	NM_001844	73.4678	COL2A1
hsa-mir-6510	NM_001190943	72.2871	TNFSF10
hsa-mir-134	NM_001844	77.4781	COL2A1
hsa-mir-4677	NM_004863	88.3559	SPTLC2
hsa-mir-4677	NM_003012	73.45515	SFRP1
hsa-mir-4677	NM_003012	58.41983	SFRP1
hsa-mir-4677	NM_001844	64.4672	COL2A1
hsa-mir-125b-2	NM_004863	81.1744	SPTLC2
hsa-mir-5586	NM_001844	86.4851	COL2A1

hsa-mir-616	NM_001193335	83.66219	ASPN
hsa-mir-222	NM_001302123	54.7001	CXCL11
hsa-mir-18a	NM_001077654	78.6758	TNFAIP8
hsa-mir-18a	NM_001844	51.9634	COL2A1
hsa-mir-495	NM_001453	65.72426	FOXC1
hsa-mir-495	NM_002775	67.9268	HTRA1
hsa-mir-495	NM_001171581	96.44696	ITM2A
hsa-mir-29b-2	NM_001077654	68.4902	TNFAIP8
hsa-mir-27b	NM_004419	73.7791	DUSP5
hsa-mir-27b	NM_004863	82.47013	SPTLC2
hsa-mir-27b	NM_003012	93.27801	SFRP1
hsa-mir-942	NM_003012	68.1522	SFRP1
hsa-mir-942	NM_004863	79.63713	SPTLC2
hsa-mir-576	NM_003012	76.7581	SFRP1
hsa-mir-376c	NM_001077654	65.51542	TNFAIP8
hsa-mir-133b	NM_001302123	50	CXCL11
hsa-mir-133b	NM_004419	76.9457	DUSP5
hsa-mir-133b	NM_001453	79.5863	FOXC1
hsa-mir-150	NM_004863	55.13409	SPTLC2
hsa-mir-7-1	NM_003012	64.3331	SFRP1
hsa-mir-511	NM_001647	83.1836	APOD
hsa-mir-511	NM_004863	84.70739	SPTLC2
hsa-mir-511	NM_001077654	64.9614	TNFAIP8
hsa-mir-511	NM_002775	62.2474	HTRA1
hsa-mir-214	NM_001190943	51.6121	TNFSF10
hsa-mir-758	NM_001278736	64.9068	CCL5
hsa-mir-758	NM_001190943	64.0171	TNFSF10
hsa-mir-758	NM_004863	55.0982	SPTLC2
hsa-mir-142	NM_004863	51.4403	SPTLC2
hsa-mir-204	NM_001453	97.1037	FOXC1
hsa-mir-204	NM_016584	62.8694	IL23A
hsa-mir-155	NM_001077654	64.1595	TNFAIP8
hsa-mir-155	NM_002164	82.2192	IDO1
hsa-mir-10b	NM_003012	73.7255	SFRP1
hsa-mir-3614	NM_001077654	87.36709	TNFAIP8
hsa-mir-487b	NM_001302123	89.14869	CXCL11
hsa-mir-29a	NM_001193335	56.2208	ASPN
hsa-mir-29a	NM_001844	97.45356	COL2A1
hsa-mir-628	NM_002775	62.15602	HTRA1
hsa-mir-215	NM_001077654	61.3624	TNFAIP8
hsa-mir-215	NM_004863	51.96964	SPTLC2
hsa-mir-330	NM_001453	55.4929	FOXC1
hsa-mir-330	NM_003012	70.2497	SFRP1
hsa-mir-655	NM_001453	81.2044	FOXC1
hsa-mir-655	NM_003012	51.4532	SFRP1

hsa-mir-19a	NM_002775	76.157	HTRA1
hsa-mir-19a	NM_003012	61.70509	SFRP1
hsa-mir-146a	NM_001278736	81.6941	CCL5
hsa-mir-146a	NM_001453	99.13475	FOXC1
hsa-mir-146a	NM_004863	59.43829	SPTLC2
hsa-mir-181c	NM_004419	70.5801	DUSP5
hsa-mir-181c	NM_001193335	73.0576	ASPN
hsa-mir-181c	NM_001190943	51.8133	TNFSF10
hsa-mir-7-2	NM_003012	64.3331	SFRP1
hsa-mir-1301	NM_001647	53.771	APOD
hsa-mir-379	NM_001302123	83.8024	CXCL11
hsa-mir-432	NM_001190943	53.58751	TNFSF10
hsa-mir-501	NM_001453	80.2884	FOXC1
hsa-mir-218-1	NM_004863	67.60088	SPTLC2
hsa-mir-301a	NM_001453	72.43312	FOXC1
hsa-mir-301a	NM_001171581	70.7526	ITM2A
hsa-mir-493	NM_001077654	80.6789	TNFAIP8
hsa-mir-3074	NM_001453	65.20962	FOXC1
hsa-mir-3074	NM_001844	52.13298	COL2A1
hsa-mir-140	NM_001302123	86.3204	CXCL11
hsa-mir-140	NM_001171581	54.9455	ITM2A
hsa-mir-145	NM_002775	81.3835	HTRA1
hsa-mir-145	NM_004863	67.75261	SPTLC2
hsa-mir-23b	NM_004863	58.86111	SPTLC2
hsa-mir-23b	NM_001453	88.2522	FOXC1
hsa-mir-23b	NM_004419	78.7952	DUSP5
hsa-mir-23b	NM_001193335	61.9589	ASPN
hsa-mir-410	NM_001190943	65.46408	TNFSF10
hsa-mir-217	NM_001077654	94.65965	TNFAIP8
hsa-mir-217	NM_004863	66.77802	SPTLC2
hsa-mir-217	NM_002775	50.98073	HTRA1
hsa-mir-217	NM_001171581	53.7001	ITM2A
hsa-mir-654	NM_001077654	58.5766	TNFAIP8

[0292] Table 18: pre-miRNAs with predicted target in 101 gene signature list having at least 70% probability.

pre-miRNA		
hsa-mir-379	hsa-mir-18a	hsa-mir-501
hsa-let-7c	hsa-mir-15b	hsa-mir-377
hsa-mir-889	hsa-mir-625	hsa-mir-299
hsa-mir-493	hsa-mir-218-2	hsa-mir-27b
hsa-mir-758	hsa-mir-3940	hsa-mir-16-1

hsa-let-7e	hsa-mir-148a	hsa-mir-616
hsa-mir-29b-2	hsa-mir-3613	hsa-mir-655
hsa-mir-4999	hsa-mir-125b-2	hsa-mir-497
hsa-mir-766	hsa-mir-370	hsa-mir-494
hsa-mir-155	hsa-mir-10b	hsa-mir-495
hsa-mir-942	hsa-mir-145	hsa-mir-1301
hsa-mir-29a	hsa-mir-502	hsa-mir-6510
hsa-mir-431	hsa-mir-133b	hsa-mir-204
hsa-mir-656	hsa-mir-4772	hsa-mir-3677
hsa-mir-3614	hsa-mir-195	hsa-mir-496
hsa-mir-4677	hsa-mir-199b	hsa-mir-218-1
hsa-mir-143	hsa-mir-483	hsa-mir-222
hsa-mir-3074	hsa-mir-454	hsa-mir-5586
hsa-mir-214	hsa-mir-147b	hsa-mir-382
hsa-mir-215	hsa-mir-381	hsa-mir-148b
hsa-mir-181d	hsa-mir-485	hsa-mir-192
hsa-mir-134	hsa-mir-146b	hsa-mir-577
hsa-mir-511	hsa-mir-29c	hsa-mir-127
hsa-mir-146a	hsa-mir-7-1	hsa-mir-19a
hsa-mir-217	hsa-mir-301a	hsa-mir-590
hsa-mir-181c	hsa-let-7b	hsa-mir-432
hsa-mir-411	hsa-mir-140	hsa-mir-32
hsa-mir-16-2	hsa-mir-487b	hsa-mir-223
hsa-mir-380	hsa-mir-505	hsa-mir-330
hsa-mir-30a	hsa-mir-340	hsa-mir-6720
hsa-mir-23b	hsa-mir-576	hsa-mir-7-2
hsa-mir-376c		

[0293] Table 19: pre-miRNAs with predicted target in DetermaIO gene list having at least 70% probability.

miRNA	Gene Accession Number	Probability of Targeting	Gene Name
hsa-mir-146b	NM_001278736	81.6941	CCL5
hsa-mir-223	NM_004863	81.1901	SPTLC2
hsa-mir-148a	NM_001844	73.4678	COL2A1
hsa-mir-485	NM_001171581	83.1959	ITM2A
hsa-mir-29c	NM_001844	97.45356	COL2A1
hsa-mir-4772	NM_002775	78.3221	HTRA1
hsa-mir-32	NM_004419	91.93814	DUSP5
hsa-mir-32	NM_001193335	84.3651	ASPN
hsa-let-7c	NM_001171581	89.4822	ITM2A

hsa-mir-299	NM_001077654	93.57209	TNFAIP8
hsa-mir-181d	NM_004419	70.5801	DUSP5
hsa-mir-181d	NM_001193335	73.0576	ASPN
hsa-mir-181d	NM_001193335	85.7785	ASPN
hsa-mir-380	NM_001453	84.3932	FOXC1
hsa-mir-889	NM_001844	95.91891	COL2A1
hsa-mir-16-1	NM_004419	74.7026	DUSP5
hsa-mir-16-1	NM_003012	72.3666	SFRP1
hsa-mir-192	NM_001193335	77.7057	ASPN
hsa-mir-3613	NM_004419	87.96533	DUSP5
hsa-mir-3613	NM_001171581	81.5659	ITM2A
hsa-mir-148b	NM_001844	73.4678	COL2A1
hsa-mir-6510	NM_001190943	72.2871	TNFSF10
hsa-mir-134	NM_001844	77.4781	COL2A1
hsa-mir-4677	NM_004863	88.3559	SPTLC2
hsa-mir-4677	NM_003012	73.45515	SFRP1
hsa-mir-125b-2	NM_004863	81.1744	SPTLC2
hsa-mir-5586	NM_001844	86.4851	COL2A1
hsa-mir-616	NM_001193335	83.66219	ASPN
hsa-mir-18a	NM_001077654	78.6758	TNFAIP8
hsa-mir-495	NM_001171581	96.44696	ITM2A
hsa-mir-27b	NM_004419	73.7791	DUSP5
hsa-mir-27b	NM_004863	82.47013	SPTLC2
hsa-mir-27b	NM_003012	93.27801	SFRP1
hsa-mir-942	NM_004863	79.63713	SPTLC2
hsa-mir-576	NM_003012	76.7581	SFRP1
hsa-mir-133b	NM_004419	76.9457	DUSP5
hsa-mir-133b	NM_001453	79.5863	FOXC1
hsa-mir-511	NM_001647	83.1836	APOD
hsa-mir-511	NM_004863	84.70739	SPTLC2
hsa-mir-204	NM_001453	97.1037	FOXC1
hsa-mir-155	NM_002164	82.2192	IDO1
hsa-mir-10b	NM_003012	73.7255	SFRP1
hsa-mir-3614	NM_001077654	87.36709	TNFAIP8
hsa-mir-487b	NM_001302123	89.14869	CXCL11
hsa-mir-29a	NM_001844	97.45356	COL2A1
hsa-mir-330	NM_003012	70.2497	SFRP1
hsa-mir-655	NM_001453	81.2044	FOXC1
hsa-mir-19a	NM_002775	76.157	HTRA1
hsa-mir-146a	NM_001278736	81.6941	CCL5
hsa-mir-146a	NM_001453	99.13475	FOXC1
hsa-mir-181c	NM_004419	70.5801	DUSP5
hsa-mir-181c	NM_001193335	73.0576	ASPN
hsa-mir-379	NM_001302123	83.8024	CXCL11
hsa-mir-501	NM_001453	80.2884	FOXC1

hsa-mir-301a	NM_001453	72.43312	FOXC1
hsa-mir-301a	NM_001171581	70.7526	ITM2A
hsa-mir-493	NM_001077654	80.6789	TNFAIP8
hsa-mir-140	NM_001302123	86.3204	CXCL11
hsa-mir-145	NM_002775	81.3835	HTRA1
hsa-mir-23b	NM_001453	88.2522	FOXC1
hsa-mir-23b	NM_004419	78.7952	DUSP5
hsa-mir-217	NM_001077654	94.65965	TNFAIP8

[0294] Further analysis determined that certain pre-miRNAs could interact with multiple genes (*e.g.*, multiple genes from the 101 gene signature and/or DetermaIO gene list). A total of 16 pre-miRNAs were found to potentially interact with only a single gene in the 101 gene signature list (Table 20) with a probability of at least 70%. A total of 42 pre-miRNAs were found to potentially interact with only a single gene in the DetermaIO gene list with a probability of at least 70% (Table 21).

[0295] Table 20: pre-miRNAs with a single predicted target in 101 gene signature list having at least 70% probability.

pre-miRNA
hsa-mir-3677
hsa-mir-342
hsa-mir-3150b
hsa-let-7e
hsa-mir-378c
hsa-mir-5586
hsa-mir-3940
hsa-mir-483
hsa-mir-454
hsa-mir-100
hsa-mir-139
hsa-mir-409
hsa-mir-7702
hsa-mir-10a
hsa-mir-337
hsa-mir-431

[0296] Table 21A: pre-miRNAs with a single predicted target in DetermaIO gene list having at least 70% probability.

miRNA	Gene Accession Number	Probability of Targeting	Gene Name
hsa-mir-146b	NM_001278736	81.6941	CCL5
hsa-mir-223	NM_004863	81.1901	SPTLC2
hsa-mir-148a	NM_001844	73.4678	COL2A1
hsa-mir-485	NM_001171581	83.1959	ITM2A
hsa-mir-29c	NM_001844	97.45356	COL2A1
hsa-mir-625	NM_003012	50.5249	SFRP1
hsa-mir-494	NM_001190943	65.46408	TNFSF10
hsa-let-7c	NM_001171581	89.4822	ITM2A
hsa-mir-496	NM_001171581	53.6328	ITM2A
hsa-mir-340	NM_001190943	56.8947	TNFSF10
hsa-mir-299	NM_001077654	93.57209	TNFAIP8
hsa-mir-380	NM_001453	84.3932	FOXC1
hsa-mir-889	NM_001844	95.91891	COL2A1
hsa-mir-5683	NM_002164	58.29101	IDO1
hsa-mir-369	NM_001193335	51.33138	ASPN
hsa-mir-148b	NM_001844	73.4678	COL2A1
hsa-mir-6510	NM_001190943	72.2871	TNFSF10
hsa-mir-134	NM_001844	77.4781	COL2A1
hsa-mir-125b-2	NM_004863	81.1744	SPTLC2
hsa-mir-5586	NM_001844	86.4851	COL2A1
hsa-mir-616	NM_001193335	83.66219	ASPN
hsa-mir-222	NM_001302123	54.7001	CXCL11
hsa-mir-29b-2	NM_001077654	68.4902	TNFAIP8
hsa-mir-576	NM_003012	76.7581	SFRP1
hsa-mir-376c	NM_001077654	65.51542	TNFAIP8
hsa-mir-150	NM_004863	55.13409	SPTLC2
hsa-mir-7-1	NM_003012	64.3331	SFRP1
hsa-mir-214	NM_001190943	51.6121	TNFSF10
hsa-mir-142	NM_004863	51.4403	SPTLC2
hsa-mir-10b	NM_003012	73.7255	SFRP1
hsa-mir-3614	NM_001077654	87.36709	TNFAIP8
hsa-mir-487b	NM_001302123	89.14869	CXCL11
hsa-mir-628	NM_002775	62.15602	HTRA1
hsa-mir-7-2	NM_003012	64.3331	SFRP1
hsa-mir-1301	NM_001647	53.771	APOD
hsa-mir-379	NM_001302123	83.8024	CXCL11
hsa-mir-432	NM_001190943	53.58751	TNFSF10
hsa-mir-501	NM_001453	80.2884	FOXC1
hsa-mir-218-1	NM_004863	67.60088	SPTLC2
hsa-mir-493	NM_001077654	80.6789	TNFAIP8
hsa-mir-410	NM_001190943	65.46408	TNFSF10
hsa-mir-654	NM_001077654	58.5766	TNFAIP8

[0297] Methods and technologies described above were further applied to analysis of mature miRNA. Gene and mature miRNA expression datasets for five cancers were downloaded from the genomic data commons (GDC) portal (https://portal.gdc.cancer.gov/) using the Genomic Data Commons package in R. Assessed cancers included Bladder Urothelial Carcinoma (BLCA), Breast invasive carcinoma (BRCA), Colon Adenocarcinoma (COAD), Lung Adenocarcinoma (LUAD), and Lung squamous cell carcinoma (LUSC). Subtype was calculated as previously described for each sample in the datasets. Cancer types (BLCA, BRCA, COAD, LUAD and LUSC) were then split so that 5% of each dataset was reserved to create a small validation set (n=97) and 95% were concatenated to create the training set (n=1875).

[0298] With the training set established, calculations were performed to generate the spearman rho correlation coefficient, between the expression of mature miRNA across all samples and the subtype (IM, M, MSL), yielding three spearman rho values. Spearman rho valuess with a p value of <.05 were removed from the set. Three lists of mature miRNAs were generated containing 75 mature miRNAs with the highest spearman rho values in a corresponding subtype (*e.g.*, 75 mature miRNAs for each of IM, M, and MSL). A total of 151 unique mature miRNAs were obtained from this assessment (Table 21B).

[0299] Table 21B: Selected mature miRNAs with highest spearman rho coefficient in IM, M, and MSL types.

Mature miRNA					
hsa-miR-375	hsa-miR-143-5p	hsa-miR-500a-3p	hsa-miR-532-3p	hsa-miR-199a-5p	hsa-miR-130a-3p
hsa-miR-146b-3p	hsa-miR-625-3p	hsa-miR-193a-5p	hsa-miR-148a-5p	hsa-miR-532-5p	hsa-miR-26a-5p
hsa-miR-150-5p	hsa-miR-93-5p	hsa-miR-30e-5p	hsa-miR-21-3p	hsa-miR-10b-5p	hsa-let-7g-5p
hsa-miR-222-3p	hsa-miR-99b-3p	hsa-miR-10a-5p	hsa-miR-148a-3p	hsa-let-7b-5p	hsa-miR-199b-3p
hsa-miR-143-3p	hsa-miR-9-5p	hsa-miR-200b-3p	hsa-miR-140-3p	hsa-miR-181b-5p	hsa-miR-425-5p
hsa-miR-221-3p	hsa-let-7c-5p	hsa-miR-127-3p	hsa-miR-155-5p	hsa-miR-214-5p	hsa-miR-379-5p
hsa-miR-199b-5p	hsa-let-7a-5p	hsa-miR-181a-2-3p	hsa-miR-30c-2-3p	hsa-miR-181c-5p	
hsa-miR-30a-5p	hsa-miR-197-3p	hsa-miR-584-5p	hsa-miR-744-5p	hsa-miR-185-5p	
hsa-miR-27b-3p	hsa-miR-16-5p	hsa-miR-186-5p	hsa-miR-29a-3p	hsa-miR-15a-5p	
hsa-miR-27b-5p	hsa-miR-345-5p	hsa-miR-92a-3p	hsa-miR-141-5p	hsa-miR-30a-3p	
hsa-miR-339-5p	hsa-miR-423-5p	hsa-miR-22-5p	hsa-miR-23b-3p	hsa-let-7e-3p	
hsa-miR-126-5p	hsa-miR-100-5p	hsa-miR-574-3p	hsa-let-7i-5p	hsa-let-7i-3p	
hsa-miR-497-5p	hsa-miR-589-5p	hsa-miR-342-3p	hsa-miR-192-5p	hsa-miR-330-5p	
hsa-miR-141-3p	hsa-miR-28-5p	hsa-miR-146b-5p	hsa-miR-203a-3p	hsa-miR-93-3p	
hsa-miR-181a-3p	hsa-miR-103a-3p	hsa-miR-152-3p	hsa-miR-423-3p	hsa-let-7d-5p	
hsa-miR-576-5p	hsa-miR-139-5p	hsa-miR-26b-5p	hsa-miR-17-3p	hsa-miR-1307-3p	
hsa-miR-23a-3p	hsa-miR-106b-5p	hsa-miR-335-3p	hsa-miR-191-5p	hsa-miR-1301-3p	

hsa-miR-145-3p	hsa-miR-101-3p	hsa-miR-148b-3p	hsa-miR-744-3p	hsa-miR-378a-3p	
hsa-miR-337-3p	hsa-miR-28-3p	hsa-miR-629-5p	hsa-miR-145-5p	hsa-miR-361-5p	
hsa-miR-151a-5p	hsa-miR-874-3p	hsa-let-7b-3p	hsa-miR-132-3p	hsa-miR-374a-3p	
hsa-miR-125a-5p	hsa-miR-199a-3p	hsa-miR-127-5p	hsa-miR-25-3p	hsa-miR-200c-3p	
hsa-miR-29c-5p	hsa-miR-652-3p	hsa-miR-339-3p	hsa-miR-24-3p	hsa-miR-1976	
hsa-miR-29b-3p	hsa-miR-425-3p	hsa-miR-193b-3p	hsa-miR-107	hsa-miR-484	
hsa-miR-128-3p	hsa-miR-181c-3p	hsa-miR-15b-5p	hsa-miR-542-3p	hsa-miR-378a-5p	
hsa-miR-34a-5p	hsa-miR-126-3p	hsa-miR-424-5p	hsa-miR-331-3p	hsa-miR-125b-5p	
hsa-miR-664a-3p	hsa-miR-223-3p	hsa-miR-766-3p	hsa-miR-99b-5p	hsa-miR-194-5p	
hsa-miR-451a	hsa-miR-21-5p	hsa-miR-29c-3p	hsa-miR-142-3p	hsa-miR-99a-5p	
hsa-miR-505-3p	hsa-miR-106b-3p	hsa-miR-30e-3p	hsa-miR-20a-5p	hsa-miR-92b-3p	
hsa-let-7e-5p	hsa-miR-134-5p	hsa-miR-17-5p	hsa-miR-361-3p	hsa-miR-210-3p	

[0300] Interquartile range (IQR) for expression was assessed for these 151 mature miRNAs to determine which mature miRNAs had a robust range of expression values. Mature miRNAs with an IQR greater than 1 were selected for additional analysis, resulting in 134 unique mature miRNAs total.

[0301] Table 21C: Selected mature miRNAs with IQR>1.

Mature miRNA				
hsa-miR-375	hsa-miR-625-3p	hsa-miR-181a-2-3p	hsa-miR-141-5p	hsa-miR-330-5p
hsa-miR-146b-3p	hsa-miR-93-5p	hsa-miR-584-5p	hsa-miR-23b-3p	hsa-miR-93-3p
hsa-miR-150-5p	hsa-miR-99b-3p	hsa-miR-92a-3p	hsa-miR-192-5p	hsa-miR-1307-3p
hsa-miR-222-3p	hsa-miR-9-5p	hsa-miR-22-5p	hsa-miR-203a-3p	hsa-miR-1301-3p
hsa-miR-143-3p	hsa-let-7c-5p	hsa-miR-574-3p	hsa-miR-423-3p	hsa-miR-378a-3p
hsa-miR-221-3p	hsa-miR-197-3p	hsa-miR-342-3p	hsa-miR-17-3p	hsa-miR-200c-3p
hsa-miR-199b-5p	hsa-miR-16-5p	hsa-miR-146b-5p	hsa-miR-191-5p	hsa-miR-1976
hsa-miR-30a-5p	hsa-miR-345-5p	hsa-miR-152-3p	hsa-miR-744-3p	hsa-miR-484
hsa-miR-27b-3p	hsa-miR-423-5p	hsa-miR-26b-5p	hsa-miR-145-5p	hsa-miR-378a-5p
hsa-miR-27b-5p	hsa-miR-100-5p	hsa-miR-335-3p	hsa-miR-24-3p	hsa-miR-125b-5p
hsa-miR-339-5p	hsa-miR-589-5p	hsa-miR-148b-3p	hsa-miR-107	hsa-miR-194-5p
hsa-miR-126-5p	hsa-miR-139-5p	hsa-miR-629-5p	hsa-miR-542-3p	hsa-miR-99a-5p
hsa-miR-497-5p	hsa-miR-106b-5p	hsa-let-7b-3p	hsa-miR-331-3p	hsa-miR-92b-3p
hsa-miR-141-3p	hsa-miR-101-3p	hsa-miR-127-5p	hsa-miR-99b-5p	hsa-miR-210-3p
hsa-miR-181a-3p	hsa-miR-874-3p	hsa-miR-339-3p	hsa-miR-142-3p	hsa-miR-130a-3p
hsa-miR-576-5p	hsa-miR-199a-3p	hsa-miR-193b-3p	hsa-miR-20a-5p	hsa-miR-199b-3p
hsa-miR-145-3p	hsa-miR-652-3p	hsa-miR-15b-5p	hsa-miR-361-3p	hsa-miR-425-5p
hsa-miR-337-3p	hsa-miR-425-3p	hsa-miR-424-5p	hsa-miR-199a-5p	hsa-miR-379-5p
hsa-miR-151a-5p	hsa-miR-181c-3p	hsa-miR-766-3p	hsa-miR-532-5p	
hsa-miR-125a-5p	hsa-miR-126-3p	hsa-miR-29c-3p	hsa-miR-10b-5p	
hsa-miR-29c-5p	hsa-miR-223-3p	hsa-miR-17-5p	hsa-let-7b-5p	

hsa-miR-29b-3p	hsa-miR-106b-3p	hsa-miR-532-3p	hsa-miR-181b-5p	
hsa-miR-128-3p	hsa-miR-134-5p	hsa-miR-148a-5p	hsa-miR-214-5p	
hsa-miR-34a-5p	hsa-miR-500a-3p	hsa-miR-21-3p	hsa-miR-181c-5p	
hsa-miR-664a-3p	hsa-miR-193a-5p	hsa-miR-148a-3p	hsa-miR-185-5p	
hsa-miR-451a	hsa-miR-30e-5p	hsa-miR-155-5p	hsa-miR-15a-5p	
hsa-miR-505-3p	hsa-miR-10a-5p	hsa-miR-30c-2-3p	hsa-miR-30a-3p	
hsa-let-7e-5p	hsa-miR-200b-3p	hsa-miR-744-5p	hsa-let-7e-3p	
hsa-miR-143-5p	hsa-miR-127-3p	hsa-miR-29a-3p	hsa-let-7i-3p	

[0302] Next, selected mature miRNAs were evaluated in real-world plasma samples. Data from GSE73002 from the NCBI gene expression omnibus (https://www.ncbi.nlm.nih.gov/geo/) were downloaded and this dataset (containing serum miRNA expression levels for breast cancer detection) were assessed for presence of selected mature miRNAs. A total of 131 unique miRNAs were identified in the dataset.

[0303] Among other things, the present Example demonstrates that available miRNA expression data may be utilized, and, in some embodiments, combined with the 101 gene signature to produce a model to classify miRNAs (*e.g.*, pre-miRNAs, mature miRNAs, combinations thereof) into a particular signature type (*e.g.*, IM, M, MSL). In some embodiments, this model may be used to assess a sample of interest (*e.g.*, tumor sample from a subject, blood and/or plasma sample from a subject) for miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) expression levels in order to assess IM, M, and MSL signature levels. In some embodiments, assessment of gene signature levels could be leveraged to create a blood-based, miRNA-specific scoring system to inform selection and/or modification of therapy (*e.g.*, ICI therapy, chemotherapy, etc.).

Example 14: Assessment of gene mutation data

[0304] The present Example, among other things, demonstrates that classifications provided herein can be correlated with gene mutation and interaction data and may be utilized for and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0305] A dataset comprising gene mutation and interaction data (*e.g.*, amino acid changes, affected protein, mutation type, participant information) was downloaded from IntAct database (https://www.ebi.ac.uk/intact/home). The dataset was analyzed for

interactions with one or more genes within the gene list described in Example 15, resulting in a list of 4285 gene mutations of interest. These gene mutations were further analyzed to identify any potential interactions with other genes within the 939 gene list, producing a list of 309 interactions of interest.

[0306] Next, identified gene mutations with interactions were assessed to determine whether certain mutations could result in altered interactions, *e.g.*, whether a wild-type protein would interact with a protein with a signature of IM, M, or MSL, and an identified mutation would interact with a protein from a different signature of IM, M, or MSL. Gene mutations were mapped to IM, M, or MSL subtypes based upon clustering analysis for each tumor sample, wherein a gene was within a certain Euclidean distance for each subtype. Gene mutations were assigned to a single subtype if (i) they clustered with one subtype based upon data from 11 or more different tumor tissue types or if (ii) they clustered with one subtype based upon data from 10 different tumor tissue types and clustered with a different subtype in 6 or less different tumor tissue types. Gene mutations were assigned to multiple subtypes if (i) they clustered with one subtype based upon data from 10 tumor tissue types and clustered with a different subtype based upon data from 7 or 8 different tumor tissue types, (ii) they clustered with one subtype based upon data from 8 or 9 tumor tissue types and clustered with a different subtype based upon data from 7-9 different tumor tissue types. Gene mutations were not given a subtype if they clustered with one subtype based upon data from 8or 9 tumor tissue types and clustered with a different subtype based upon data from 6 or less different tumor tissue types.

[0307] After assignment of subtypes, gene mutations were filtered to identify interactions between genes (*e.g.*, interactions of expressed mutant protein with a wild-type or mutant protein of interest) wherein a gene of one subtype interacted with a gene of another subtype. A total of 92 gene mutations of interest were identified as a result of this analysis. Gene mutations with no predicted effect were then removed, producing a list of 64 gene mutations of interest (Table 22). Mutation descriptions in Table 22 are presented in formatting as outlined in IntAct database (https://www.ebi.ac.uk/intact/download/datasets#mutations).

[0308] Table 22: Gene mutations interacting with one or more genes of a different subtype.

Affected protein symbol	Affected Gene Subtypes	Feature type	Interactions
HTRA1	M	mutation(MI:0118)	['HTRA4 : IM']
LPL	M	mutation(MI:0118)	['GPIHBP1 : MSL']
MPP1	IM	mutation(MI:0118)	['GYPC : MSL']
HTRA4	IM	mutation(MI:0118)	['HTRA1 : M']
FGFR1	M	mutation(MI:0118)	['FGF2 : MSL_M']
GUCY1B1	MSL_M	mutation(MI:0118)	['GUCY1A1 : MSL']
GNAO1	M	mutation(MI:0118)	['GNG2 : MSL']
PILRA	IM	mutation(MI:0118)	['SORCS1 : MSL_M']
CCL5	IM	mutation(MI:0118)	['CXCL12 : MSL']
GYPC	MSL	mutation(MI:0118)	['MPP1 : IM']
ADAM8	IM	mutation(MI:0118)	['SNX33 : M']
PLEK	IM	mutation(MI:0118)	['CAVIN2 : MSL', 'F13A1 : MSL']
PLEK	IM	mutation(MI:0118)	['ACTN1 : M']
BTK	IM	mutation decreasing(MI:0119)	['GTF2I : M']
FYN	MSL	mutation decreasing(MI:0119)	['PRKCQ : IM']
GPIHBP1	MSL	mutation decreasing(MI:0119)	['LPL : M']
BTK	IM	mutation decreasing(MI:0119)	['SH3BP5 : MSL_M']
IGFBP5	M	mutation decreasing(MI:0119)	['IGF1 : MSL']
CFH	MSL	mutation decreasing(MI:0119)	['C3 : IM_MSL']
LAT	IM	mutation decreasing(MI:0119)	['PLCG1 : M']
NOD2	IM	mutation decreasing strength(MI:1133)	['VIM : MSL']
LILRB2	IM	mutation decreasing strength(MI:1133)	['ANGPTL2 : M']
APOE	IM	mutation decreasing strength(MI:1133)	['LRP1 : M']
PRKN	M	mutation decreasing strength(MI:1133)	['UBE2L6 : IM']
LRP1	M	mutation decreasing strength(MI:1133)	['APOE : IM']
NTRK3	MSL	mutation decreasing strength(MI:1133)	['DOK6 : M']
LRP1	M	mutation decreasing strength(MI:1133)	['APOE : IM']
THEMIS	IM	mutation decreasing strength(MI:1133)	['PLCG1 : M']
FOXP3	IM	mutation disrupting(MI:0573)	['RBPMS : M']
WARS1	IM	mutation disrupting(MI:0573)	['CDH5 : MSL']
VCAM1	IM	mutation disrupting(MI:0573)	['SPTBN1 : M', 'APOE : IM', 'TLN1 : M', 'PSMA3 : IM', 'S100A8 : IM', 'PSMA6 : IM']
CFH	MSL	mutation disrupting(MI:0573)	['C3 : IM_MSL']
SH2D1B	IM	mutation disrupting(MI:0573)	['INPP5D : IM', 'DAPP1 : IM', 'PECAM1 : MSL', 'CD84 : IM']
PLCG1	M	mutation disrupting(MI:0573)	['MAP4K1 : IM']
FOXP3	IM	mutation disrupting(MI:0573)	['RBPMS : M']
LY96	IM	mutation disrupting(MI:0573)	['TLR4 : IM_MSL']
VCAM1	IM	mutation disrupting(MI:0573)	['TLN1 : M', 'VCL : M', 'PSMA3 : IM', 'FERMT3 : IM', 'PSMA6 : IM']
VCAM1	IM	mutation disrupting(MI:0573)	['TLN1 : M']
VCAM1	IM	mutation disrupting(MI:0573)	['KIDINS220 : M', 'TMPO : IM_M', 'TLN1 : M', 'PSMA3 : IM', 'PSMA6 : IM', 'HIP1 : M', 'FLNC : M', 'SPTBN1 : M']
HTRA1	M	mutation disrupting rate(MI:1129)	['HTRA4 : IM']

CTNNA3	M	mutation disrupting strength(MI:1128)	['USHBP1 : MSL']
LPL	M	mutation disrupting strength(MI:1128)	['GPIHBP1 : MSL']
FAM107A	MSL	mutation disrupting strength(MI:1128)	['CCDC136 : M']
PRKN	M	mutation disrupting strength(MI:1128)	['UBE2L6 : IM']
BTK	IM	mutation disrupting strength(MI:1128)	['MEOX2 : MSL']
NTRK3	MSL	mutation disrupting strength(MI:1128)	['DOK6 : M']
PRKN	M	mutation disrupting strength(MI:1128)	['NFKBIE : IM']
LILRB2	IM	mutation disrupting strength(MI:1128)	['ANGPTL2 : M']
ESR1	IM_MSL	mutation disrupting strength(MI:1128)	['ESR2 : IM_M']
PILRA	IM	mutation disrupting strength(MI:1128)	['PIANP : M']
NTRK3	MSL	mutation disrupting strength(MI:1128)	['NTF3 : M', 'DOK6 : M']
APOE	IM	mutation disrupting strength(MI:1128)	['LRP1 : M']
DPYSL2	MSL_M	mutation disrupting strength(MI:1128)	['DPYSL3 : M']
DNMT3A	M	mutation disrupting strength(MI:1128)	['TCL1A : IM']
GPIHBP1	MSL	mutation disrupting strength(MI:1128)	['LPL : M']
PBXIP1	M	mutation disrupting strength(MI:1128)	['ESR1 : IM_MSL']
ESR1	IM_MSL	mutation disrupting strength(MI:1128)	['STAT1 : IM']
LDOC1	M	mutation disrupting strength(MI:1128)	['FAM107A : MSL']
SELP	MSL	mutation increasing(MI:0382)	['SELPLG : IM']
LILRB2	IM	mutation increasing strength(MI:1132)	['ANGPTL2 : M']
KDR	MSL	mutation increasing strength(MI:1132)	['ANTXR1 : M']
ANTXR1	M	mutation increasing strength(MI:1132)	['KDR : MSL']
PILRA	IM	mutation increasing strength(MI:1132)	['PIANP : M']
FGFR1	M	mutation increasing strength(MI:1132)	['FGF2 : MSL_M']

[0309] Among other things, the present Example demonstrates that gene mutations and/or interactions may be assessed to determine potential interactions with genes of interest that map to one or more of the IM, M, and MSL subtypes (*e.g.*, genes from the 101-gene signature list, DetermaIO list, and/or larger gene sets based upon clustering with the 101-gene signature list). In some embodiments, certain gene mutations that map to one subtype (*e.g.*, IM, M, MSL) may be identified as having potential interactions with one or more genes of interest mapping to a different subtype (*e.g.*, IM, M, MSL). In some embodiments, such gene mutations may be used to inform treatment of a subject. For example, in some embodiments, treatment targeting or inhibiting a mutated gene having one signature (*e.g.*, M, MSL) that interacts with a gene having a different signature (*e.g.*, IM) could produce an increase in overall IM signature for a tumor and result in an increased IO score. In some embodiments, treatment targeting or inhibiting mutated gene having one signature (*e.g.*, IM) that interacts with a gene having a different signature (*e.g.*, M, MSL) could produce an increase in overall M or MSL signature for a tumor and result in a decreased IO score. In

some embodiments, information obtained from gene mutation assessment can be used to inform selection and/or modification of therapy, and particularly of combination therapies (e.g., additional therapy in combination with ICI therapy). In some embodiments, information obtained from gene mutations can be used to inform selection and/or modification of therapy, and particularly of combination therapies (e.g., additional therapy in combination with ICI therapy) based upon changes in IO scoring. In some embodiments, treatment targeting or inhibiting mutated genes could be combined with one or more therapies (*e.g.*, chemotherapy, ICI, etc.) based upon changes in IO scoring. In some embodiments, treatment targeting or inhibiting a mutated gene (*e.g.*, via one or more of an antibody, small molecule, antibody conjugate, etc.) could be targeted to one or more regions the corresponding expressed protein (*e.g.*, one or more regions that is/are associated with mutation).

[0310] In some embodiments, the present example demonstrates that certain gene mutations (*e.g.*, mutation in FGFR1) may associate with the M subtype and/or may increase affinity for one or more genes in the MSL subtype (*e.g.*, MSL). In some embodiments, increased interactions between or among genes in M and MSL subtypes may promote reduced tumor responsiveness to one or more therapies. Accordingly, in some embodiments, the present disclosure teaches that a treatment may be selected specifically targeting such gene mutations; without wishing to be bound by any particular theory, the present disclosure teaches that administering such targeted treatment (and, in some embodiments, admninistering such in combination with IO therapy), may provide improved subject outcome as compared to a non-targeted therapy and/or to IO therapy alone.

[0311] In some embodiments, the present example demonstrates that certain gene mutations (*e.g.*, mutation in SELP) may associate with the MSL subtype and increase affinity for one or more genes in the IM subtype (*e.g.*, MSL). In some embodiments, a treatment may be selected specifically targeting such gene mutations, for example in order to increase expression of genes associated with IM (*e.g.*, potentially increasing IM subtype character of a tumor and/or DetermaIO scoring).

Example 15: Assessment of compound sensitivity

[0312] The present Example, among other things, demonstrates that classifications provided herein can be correlated with compound sensitivity data and may be utilized for

and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0313] Datasets of tumor sensitivity to various compounds as part of the PRISM screen were downloaded (https://depmap.org/portal/download/). Compounds were annotated with compound names and mechanisms of action based upon publicly available data. Analysis was restricted to cell line assays not annotated as 'Failed', resulting in a total of 568 cell lines and 4686 compounds. Gene expression data for a set of 19177 genes on 1389 cell lines was also acquired from the Broad Institute (https://depmap.org/portal/download/). Cell lines in the gene expression data set were split into 2/3 training and 1/3 test sets, balanced for cell lineage, using the 'caret' package in R version 4.1.1. Cells were classified by subtype (*e.g.*, IM, M, MSL), as described herein using the 101 gene signature. Data was limited to cell lines that were included in the gene expression training set and were also employed in the compound sensitivity screen. This resulted in a set of 4686 compounds applied to 371 cell lines. The test set consisted of 4686 compounds applied to 188 cell lines.

[0314] Compounds were limited to those with a significant (p value <0.05) negative correlation with the IM, MSL or M subtypes, determined by classifying cell lines using the 101 gene signatures as previously herein, and then correlating the compound sensitivity scores with the subtype correlations across the training and test sets of cell lines. Only compounds with a correlation of less than -0.1 with at least one subtype correlation in the training cell set were retained for further analysis. This resulted in a set of 598 compounds, some of which were not uniformly associated with the different subtypes (Table 23A).

[0315] Table 23A: Compounds with at least one subtype correlation in training cell set.

BROAD compound ID	Compound Name	Mechanism of Action	TNB CType train	DTIO Corr train	IM Corr test	MSL Corr test	M Corr test	DTIO Corr test
A00077618	8-bromo-cGMP	PKA activator	MSL	0.074852	-0.00708	-0.05953	-0.06633	-0.017
A00842753	oleuropein	estrogen receptor agonist	MSL	-0.00213	0.035013	-0.08668	-0.08237	0.021715
A04497688	trilostane	3beta-hydroxy-delta5-steroid dehydrogenase inhibitor	MSL	-0.01163	-0.099	-0.00526	0.01632	-0.05152
A09472452	flecainide	sodium channel blocker	IM	-0.16563	-0.0668	0.045385	-0.00817	-0.0192
A10523515	GSK429286A	rho associated kinase inhibitor	MSL	-0.00189	0.070284	-0.17861	-0.16057	0.102994
A10773072	glycerol-monolaurate	beta lactamase inhibitor	M	0.048439	0.223193	-0.11751	-0.22188	0.143213
A10977446	carvedilol	adrenergic receptor antagonist	IM	-0.08384	-0.04298	-0.07456	0.045591	0.000729
A11990600	lorazepam	benzodiazepine receptor agonist	IM	-0.13184	-0.08811	0.090871	0.097022	-0.02916
A12230535	nutlin-3	MDM inhibitor	M	0.160633	0.06852	0.035363	-0.07413	0.150256
A12454076	L-Hydroxyproline		IM	-0.0814	-0.01657	-0.15111	-0.01403	-0.05682
A14886633	norgestrel	progesterone receptor agonist	M	0.080278	0.057726	9.57E-05	-0.14398	0.045486
A16263897	misonidazole		MSL	-0.00067	-0.1232	-0.0539	0.078077	-0.138
A17009129	isavuconazole	cytochrome P450 inhibitor	MSL	0.080655	0.107481	-0.1043	-0.06544	0.043623
A18992208	lercanidipine	calcium channel blocker	IM	-0.10567	-0.05125	0.056732	0.064398	0.040143
A19736161	ondansetron	serotonin receptor antagonist	IM	-0.07634	-0.1174	-0.01358	0.062424	-0.11235
A19777893	menadione-bisulfite	vitamin K	M	0.003549	0.192533	-0.10861	-0.20263	0.136223
A23124853	PF-06463922	ALK tyrosine kinase receptor inhibitor	MSL	-0.07689	-0.12186	-0.05668	-0.02078	-0.00728
A23127772	sclareol		MSL	0.027899	-0.0091	-0.00812	0.006849	-0.02449
A23418262	floctafenine	cyclooxygenase inhibitor	MSL	-0.0399	0.041975	-0.04168	-0.04815	0.127147
A24514565	warfarin	vitamin K antagonist	M	0.141944	-0.00917	-0.02248	-0.08567	0.068712
A24587114	isoetharine	adrenergic receptor agonist	IM	-0.15006	-0.06951	0.0084	-0.01333	-0.05616
A25004090	erastin	ion channel antagonist	MSL	-0.08613	-0.13507	-0.07532	0.020114	-0.06388

A27883417	alexidine	phosphatidylglycerophosphatase inhibitor	M	0.209638	0.162958	0.011116	-0.14599	0.100148
A28970875	puromycin	protein synthesis inhibitor	M	0.027776	0.064756	0.012902	-0.11839	0.066029
A29520968	acifran	cholesterol inhibitor	IM	-0.02068	-0.0076	0.126024	0.002814	-0.00246
A29700858	carbenoxolone	11-beta hydroxysteroid dehydrogenase inhibitor	IM	-0.07689	-0.06543	-0.01512	0.00454	-0.05769
A30590053	MR-16728	acetylcholine release enhancer	IM	-0.16056	-0.01298	0.064867	0.025101	0.043526
A30886737	florfenicol	protein synthesis inhibitor	M	0.077868	0.082266	0.003813	-0.06536	0.130946
A31811760	miltefosine	membrane integrity inhibitor	IM	-0.02111	-0.06197	0.091874	0.016792	-0.04486
A33711280	metixene	acetylcholine receptor antagonist	IM	-0.14865	-0.09271	0.106076	0.113219	-0.04991
A34255068	rolipram	phosphodiesterase inhibitor	IM	-0.13204	-0.16867	0.120148	0.145406	-0.11127
A36057565	bruceantin	protein synthesis inhibitor	M	-0.00997	-0.02817	0.041762	-0.01138	-0.09134
A36074203	remacemide	glutamate receptor antagonist	IM	-0.09407	-0.00275	0.012004	-0.03609	-0.0384
A36267905	buphenine	adrenergic receptor agonist	IM	-0.13436	-0.07524	0.078744	0.077779	-0.05463
A40084411	CGP-12177	adrenergic receptor agonist	IM	-0.03736	-0.08055	-0.03092	0.023091	-0.06572
A40940854	ibuproxam	cyclooxygenase inhibitor; prostaglandin inhibitor	M	0.110699	-0.02197	0.073601	-0.04584	-0.12705
A41698174	bacampicillin	bacterial cell wall synthesis inhibitor	MSL	0.028395	0.044536	-0.07656	-0.07737	0.079115
A42270467	tenatoprazole	ATPase inhibitor	MSL	0.114311	0.047184	-0.05139	0.019855	0.004184
A43999749	homatropine-methylbromide	acetylcholine receptor antagonist	M	0.050905	0.063393	-0.01662	-0.00694	0.016977
A44181516	flumecinol		MSL	0.02706	0.064037	-0.09398	-0.06491	0.037858
A44188509	AZD1446	acetylcholine receptor agonist	MSL	-0.01778	-0.01023	-0.09838	-0.00226	-0.00648
A44511856	ginsenoside-rg3	angiogenesis inhibitor; apoptosis stimulant	M	0.056597	0.007852	-0.02955	-0.05841	-0.00056
A44971162	ODM-201	androgen receptor antagonist	MSL	0.003412	-0.03339	-0.13807	0.043792	-0.01761
A45889380	mepacrine	cytokine production inhibitor; NFkB pathway inhibitor; TP53 activator	IM	-0.17027	-0.10962	0.208632	0.183871	-0.04932
A50675490	carazolol	adrenergic receptor antagonist	MSL	0.050713	-0.1204	-0.02083	0.041574	-0.06042
A51747092	moprolol	adrenergic receptor antagonist	IM	-0.14525	-0.07275	-0.02538	-0.00898	-0.14209
A52660433	tetrindole	monoamine oxidase inhibitor	IM	-0.09692	-0.02376	0.060719	0.06046	-0.04907
A55312468	k-strophanthidin	ATPase inhibitor	MSL	-0.01124	-0.06974	-0.10988	-0.03165	-0.03307
A55484088	BNTX	opioid receptor antagonist	IM	-0.1416	-0.13712	0.106241	0.093233	-0.10848

A56085258	LGX818	RAF inhibitor	M	0.095349	0.222544	0.162724	-0.23255	0.14417
A56241705	trimethoquinol	adrenergic receptor antagonist	MSL	-0.0983	-0.06802	-0.05303	-0.00108	-0.05537
A56359832	zileuton	leukotriene synthesis inhibitor; lipoxygenase inhibitor	MSL	-0.00728	0.067338	-0.05561	-0.06242	0.13867
A56675431	althiazide	diuretic	M	-0.02356	0.043864	-0.10294	-0.07072	0.080778
A58947127	AMG319	PI3K inhibitor	MSL	-0.03859	0.079864	-0.08814	-0.17127	0.032831
A59378440	butylphthalide	potassium channel antagonist	MSL	0.011784	-0.03693	-0.02003	-0.03289	-0.10822
A59961917	BQ-123	endothelin receptor antagonist	MSL	0.04394	0.044903	-0.14206	-0.13738	0.076412
A64610707	pranoprofen	cyclooxygenase inhibitor	M	0.100929	0.061883	-0.10549	-0.07721	-0.01897
A64743628	isomethептene-mucate		IM	-0.11792	-0.09289	0.117989	0.05313	-0.04443
A68083442	pranidipine	calcium channel blocker	M	0.103012	0.012969	-0.01285	-0.08946	0.040504
A69917777	aminopentamide	acetylcholine receptor antagonist	MSL	0.018261	-0.00471	-0.07475	-0.04959	-0.03995
A71033472	fendiline	calcium channel blocker	IM	-0.16084	-0.12538	-0.04896	0.112397	-0.11301
A71407503	imimur	other antifungal	IM	-0.08883	-0.09878	0.031385	0.038736	-0.04743
A72297358	ozolinone	diuretic	MSL	0.043059	-0.13218	-0.06039	-0.01029	-0.09683
A72401848	gadoteridol	radiopaque medium	MSL	-0.04116	-0.02624	-0.00929	-0.02135	-0.08228
A73679382	MK-571	leukotriene receptor antagonist	MSL	0.024321	-0.02535	-0.00401	-0.02967	-0.00581
A75479906	rimantadine	antiviral; RNA synthesis inhibitor	IM	-0.0701	-0.13735	0.124737	0.121882	-0.05017
A75769826	SDM25N	opioid receptor antagonist	IM	-0.12001	-0.16816	-0.06407	0.088071	-0.16502
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	M	0.119134	0.263708	-0.01663	-0.24548	0.165805
A78341343	regadenoson	adenosine receptor agonist	IM	-0.15857	-0.08832	-0.05759	0.02954	-0.10154
A78877355	nefopam	cyclooxygenase inhibitor	IM	-0.13132	-0.14884	-0.12309	0.021929	-0.14163
A79803969	memantine	glutamate receptor antagonist	IM	-0.03846	-0.20725	0.101963	0.159677	-0.1964
A80213327	NSC-23766	Ras GTPase inhibitor	M	0.067501	-0.00484	0.133217	-0.06657	0.047997
A80280426	AD-5467	aldose reductase inhibitor	MSL	0.018022	-0.0506	-0.05143	0.039021	-0.04673
A81370665	BI-D1870	ribosomal protein inhibitor	IM	-0.09163	-0.01584	0.020052	0.010011	0.018544
A82522119	tibolone	androgen receptor agonist; estrogen receptor agonist; progesterone receptor agonist	IM	-0.11619	-0.09026	-0.06141	-0.05265	-0.05238
A84810646	ginsenoside-rd	calcium channel blocker	MSL	-0.02011	-0.05744	-0.02352	-0.00784	-0.0392

A85025557	NCS-382	GABA receptor antagonist	IM	-0.13426	-0.09394	0.059282	0.105905	-0.17053
A86871940	nicaraven	free radical scavenger	IM	-0.12278	-0.05557	0.071825	-0.00159	0.039544
A88562598	degarelix	gonadotropin releasing factor hormone receptor antagonist	MSL	0.019957	0.000275	-0.05421	-0.03554	-0.01776
A92630576	trimebutine	opioid receptor agonist	M	-0.00435	0.02851	-0.03839	-0.0841	-0.05432
A92872453	N-acetylmannosamine		IM	-0.0802	-0.09969	-0.06809	0.083615	-0.05912
A96456596	FPL-55712	leukotriene receptor antagonist	IM	-0.1264	-0.05838	0.075493	0.133834	-0.01746
A97739905	ketoprofen	cyclooxygenase inhibitor	MSL	0.060339	-0.06437	-0.01815	0.051319	0.01612
A98845662	desvenlafaxine	serotonin norepinephrine reuptake inhibitor (SNRI)	IM	-0.16436	-0.09107	0.048536	0.047545	-0.04076
K01039503	sofalcone	mucus protecting agent	IM	-0.05742	-0.05509	0.114824	0.04839	0.045539
K01291782	molidustat	hypoxia inducible factor inhibitor	IM	-0.12926	-0.10307	-0.046	0.151199	-0.08823
K01507359	rifampin	RNA polymerase inhibitor	M	0.115452	0.110211	-0.11515	-0.18692	0.057333
K01624185	maltobionic-acid	matrix metalloprotease inhibitor	M	0.09859	0.107806	0.037165	-0.08169	0.130029
K01942991	oxotremorine-m	acetylcholine receptor agonist	IM	-0.0669	-0.08895	0.097283	0.059918	-0.11284
K02113016	olaparib	PARP inhibitor	M	0.026605	0.05691	-0.10496	-0.11335	0.064041
K02152879	sivelestat	elastase inhibitor	IM	-0.10576	-0.00698	0.06219	0.007744	0.049544
K02594908	sulfanilamide	carbonic anhydrase inhibitor	MSL	-0.03491	0.054725	-0.01366	0.006753	0.023484
K02750403	piboserod	serotonin receptor antagonist	MSL	0.011882	-0.02493	-0.05998	0.008828	0.020963
K02965577	secalciferol	vitamin D receptor agonist	IM	-0.06151	-0.12541	-0.05502	0.078662	-0.09515
K03063480	PF-477736	CHK inhibitor	M	-0.01779	0.057954	-0.10663	-0.16439	-0.03209
K03164761	thiazovivin	rho associated kinase inhibitor	MSL	0.033738	0.039098	-0.21347	-0.10822	0.048453
K03289018	CCT137690	Aurora kinase inhibitor	M	-0.02552	-0.03424	-0.02426	-0.09289	-0.13958
K03384561	roquinimex	angiogenesis inhibitor; tumor necrosis factor production inhibitor	IM	-0.09623	-0.00663	0.030006	-0.00406	0.023981
K03503561	ravuconazole	sterol demethylase inhibitor	MSL	0.098854	0.028167	-0.00902	-0.01521	-0.03731
K03739921	hypoxanthine	PARP inhibitor	MSL	0.021509	0.031275	-0.2363	-0.03639	-0.01455
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	IM	-0.1539	-0.18202	0.364371	0.231003	-0.05086
K04264130	favipiravir	RNA polymerase inhibitor	IM	-0.12869	-0.03139	0.094929	-0.04351	0.002354
K04394237	drospirenone	mineralocorticoid receptor antagonist	M	0.10521	0.118209	0.004094	-0.08392	0.072095

K04568635	octenidine	membrane integrity inhibitor	M	0.147947	0.164049	0.028498	-0.21749	0.09423
K04603573	1,12-Besm	polyamine biosynthesis inhibitor	M	0.07515	-0.00575	-0.13217	-0.0837	0.020164
K04623885	BIBR-1532	telomerase inhibitor	MSL	-0.05255	-0.17124	-0.14817	0.140976	-0.22597
K05048137	phytosphingosine		IM	-0.10885	-0.06346	0.017576	0.066885	0.004108
K05445342	WP1066	STAT inhibitor	IM	-0.08426	-0.15525	0.075395	0.129476	-0.129
K05619559	tobramycin	bacterial 30S ribosomal subunit inhibitor	IM	-0.08252	-0.03111	-0.10534	-0.017	-0.03868
K05638300	sevoflurane	membrane integrity inhibitor	IM	-0.12131	-0.03476	-0.05768	0.007586	-0.09134
K05674516	sofosbuvir	RNA polymerase inhibitor	IM	-0.06249	-0.00524	-0.06006	-0.06371	0.021008
K05804044	AZ-628	RAF inhibitor	M	0.190801	0.335575	0.113257	-0.23266	0.324717
K05900209	dexlansoprazole	ATPase inhibitor	M	0.13562	0.067482	-0.03546	-0.02941	0.057768
K06328344	bremelanotide	melanocortin receptor agonist	IM	-0.07952	-0.04735	-0.04913	0.07264	-0.06366
K06388517	lofemizole	cyclooxygenase inhibitor	MSL	0.065259	0.067703	-0.15975	-0.10659	0.036188
K06519765	vinblastine	microtubule inhibitor; tubulin polymerization inhibitor	MSL	-0.10207	-0.09395	-0.06392	-0.05208	-0.08085
K06543683	bisindolylmaleimide-ix	PKC inhibitor	M	0.188652	0.225538	0.012389	-0.23095	0.162738
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	IM	-0.07697	-0.19006	0.419057	0.277631	-0.02871
K07487750	WHI-P154	JAK inhibitor	IM	-0.12449	-0.227	0.215164	0.246617	-0.06543
K07612980	sparfloxacin	bacterial DNA gyrase inhibitor	IM	-0.14733	-0.10947	0.132562	0.10192	-0.10417
K07625016	norethisterone-enanthate	contraceptive agent	IM	-0.1312	-0.05873	0.104245	0.017742	0.009756
K07691486	roscovitine	CDK inhibitor	IM	-0.04702	-0.21186	0.147224	0.093376	-0.16505
K08542803	gambogic-acid	caspase activator	M	-0.03027	0.068122	-0.05664	-0.16814	-0.00196
K08799216	pelitinib	EGFR inhibitor	IM	-0.13352	-0.11387	0.308393	0.196564	-0.03925
K08893438	CCG-50014	G protein signaling inhibitor	M	0.040398	0.039636	-0.20627	-0.11977	-0.03813
K08953028	U-0521	catechol O methyltransferase inhibitor	IM	-0.11147	-0.0012	0.062564	0.027492	-0.01537
K09090523	firocoxib	cyclooxygenase inhibitor	IM	-0.05889	-0.06912	0.049743	0.0558	-0.0068
K09295674	carzenide		IM	-0.06454	-0.00369	0.024693	0.030621	0.002858
K09397065	SR-57227A	serotonin receptor agonist	IM	-0.10476	-0.02879	-0.00449	-0.08168	0.016349
K09416995	lovastatin	HMGCR inhibitor	M	0.051166	0.131404	-0.1344	-0.27624	0.05706

K09436144	YM022	CCK receptor antagonist	M	0.038839	-0.00497	-0.08788	-0.05702	-0.00858
K09602097	forskolin	adenylyl cyclase activator	IM	-0.06089	-0.0681	-0.02751	0.028847	-0.05334
K09951645	dabrafenib	RAF inhibitor	M	0.043133	0.163112	-0.02177	-0.23346	0.14386
K10065684	dantron	laxative	MSL	-0.0095	-0.03924	-0.02064	0.094016	-0.05325
K10670311	sulfasalazine	cyclooxygenase inhibitor	IM	-0.10126	-0.11737	-0.04249	0.087243	-0.03952
K10706131	rivastigmine	acetylcholinesterase inhibitor	IM	-0.05647	-0.22825	0.041894	0.155955	-0.24721
K11071038	ICI-162846	histamine receptor antagonist	IM	-0.09255	-0.15372	0.051701	0.164712	-0.05711
K11094367	acetanilide	hydrogen peroxide decomposition inhibitor	IM	-0.10712	-0.16111	0.069008	0.076528	-0.10671
K11443721	NE-100	sigma receptor antagonist	MSL	0.093195	0.023282	-0.07257	-0.05032	0.025876
K11717138	benzbromarone	chloride channel blocker	IM	-0.04729	-0.08532	0.031444	0.011952	-0.0086
K11900042	methylthiouracil		IM	-0.05914	-0.19355	0.129781	0.131068	-0.1781
K12040459	AT7867	AKT inhibitor	MSL	0.048117	0.046025	-0.11418	-0.16648	0.003574
K12261274	zaltidine	histamine receptor antagonist	IM	-0.15234	-0.04172	-0.03658	0.025681	-0.09292
K12829205	mechlorethamine	DNA inhibitor	IM	-0.15666	-0.07571	0.085438	0.069184	-0.05962
K13044802	ciclopirox	membrane integrity inhibitor	IM	-0.15742	-0.0735	0.084523	0.04419	-0.06749
K13060017	UNC0631	histone lysine methyltransferase inhibitor	M	0.105455	0.216782	-0.09072	-0.32562	0.163017
K13169950	NSC-3852	HDAC inhibitor	M	0.093556	0.064254	-0.09058	-0.16656	-0.00012
K13183738	pentamidine	anti-pneumocystis agent	M	0.215745	0.206933	-0.0345	-0.22166	0.139961
K13387373	thonzonium	ATPase inhibitor	M	0.156672	0.143061	0.105866	-0.13758	0.082616
K13394247	radafaxine	dopamine norepinephrine reuptake inhibitor	M	0.059801	-0.03966	-0.18176	-0.12571	-0.04236
K13486660	sulfacarbamide		IM	-0.09211	-0.02159	-0.06285	-0.02112	0.061664
K13533483	cyclosporine	calcineurin inhibitor	IM	-0.11227	-0.12262	0.261027	0.22077	-0.05214
K13646352	midostaurin	FLT3 inhibitor; KIT inhibitor; PKC inhibitor	MSL	-0.13545	-0.04213	-0.10689	-0.0718	-0.0893
K13664493	naphthoquine-phosphate	antimalarial agent	MSL	0.032118	-0.01598	-0.02275	0.034434	0.045174
K14276241	daucosterol	apoptosis stimulant	MSL	-0.04126	0.01292	-0.05449	-0.01266	0.044865
K14385366	FG-4592	hypoxia inducible factor prolyl hydroxylase inhibitor	IM	-0.07927	-0.0646	0.048589	0.051068	0.023371
K14571191	zometapine		MSL	0.091461	-0.13468	-0.04215	0.046023	-0.08271

K14796088	berberine	LDL receptor activator	M	0.109367	0.210348	0.061263	-0.15578	0.215589
K15025317	BAY-11-7082	NFkB pathway inhibitor	M	-0.00647	0.077933	0.031696	-0.14739	0.040136
K15164005	apoptosis-activator-II	carboxylesterase inhibitor	MSL	0.027079	0.103711	-0.18862	-0.14548	0.07557
K15179879	carfilzomib	proteasome inhibitor	IM	-0.13982	-0.0442	0.121707	0.012663	0.008413
K15318383	ammonium-glycyrrhizinate	thrombin inhibitor	IM	-0.06692	-0.02605	0.097102	0.050095	-0.07896
K15327298	fmoc-l-leucine	PPAR receptor agonist	M	0.089354	-0.05134	0.022971	-0.01114	-0.03928
K15563106	phloretin	sodium/glucose cotransporter inhibitor	MSL	0.024439	0.021695	-0.00079	-0.06264	-0.04132
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	M	0.148517	0.047451	-0.04621	-0.17431	0.090307
K16730910	regorafenib	FGFR inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; RAF inhibitor; RET tyrosine kinase inhibitor; VEGFR inhibitor	M	0.096675	0.167977	0.108553	-0.16788	0.127004
K17075857	chloroxine	opioid receptor antagonist	MSL	0.006831	-0.03689	-0.01788	0.016492	0.035386
K17203476	LY2874455	FGFR antagonist	IM	-0.14489	-0.01933	-0.10214	-0.0758	-0.0838
K17223896	chloroxylenol	ATP synthase inhibitor	IM	-0.10003	-0.04482	0.08067	0.1329	-0.04417
K17294426	clebopride	dopamine receptor antagonist	IM	-0.08216	-0.01282	-0.03223	0.070657	0.012136
K17497770	butein	EGFR inhibitor; src inhibitor	MSL	-0.01064	0.107801	-0.08886	-0.15379	0.054997
K17702546	PD-168393	EGFR inhibitor	IM	-0.14035	-0.09474	0.313213	0.204165	0.051791
K17849083	tranilast	angiogenesis inhibitor	IM	-0.16643	-0.04394	-0.01337	-0.01518	-0.05076
K18424115	TG-100572	src inhibitor; VEGFR inhibitor	MSL	0.090482	0.013923	-0.04088	-0.05751	0.032211
K18779551	bifemelane	acetylcholine release enhancer	IM	-0.08356	-0.05315	-0.04947	0.052284	-0.05356
K18849474	dalcetrapib	cholesteryl ester transfer protein inhibitor	IM	-0.05336	-0.04114	-0.09318	0.036301	0.053092
K18898553	salvianolic-acid-B	metalloproteinase inhibitor; EGFR inhibitor	MSL	-0.10921	0.001211	-0.06128	-0.08646	0.002256
K19061412	mubritinib	protein tyrosine kinase inhibitor	M	0.095448	0.114313	0.061376	-0.09164	0.109507
K19111024	clofibric-acid	PPAR receptor agonist	MSL	0.111623	0.023677	-0.12595	-0.05105	0.054907
K19180152	meprobamate		IM	-0.15038	-0.04138	-0.11396	-0.02222	0.004344
K19333160	RKI-1447	rho associated kinase inhibitor	MSL	0.046328	0.093793	-0.20818	-0.1921	0.081223
K19540840	saracatinib	src inhibitor	IM	-0.18309	-0.17375	0.216987	0.210625	-0.10679
K19605405	ZM-241385	adenosine receptor antagonist	IM	-0.06844	-0.15131	0.027386	0.159487	-0.06032

K19687926	lapatinib	EGFR inhibitor	IM	-0.08369	-0.12972	0.393376	0.251921	-0.0302
K20093108	BMS-587101	integrin antagonist	MSL	0.019858	-0.05699	-0.03676	0.136695	-0.08591
K20285085	R406	SYK inhibitor	MSL	-0.1076	-0.00181	-0.05554	-0.02564	-0.04153
K20372197	droxidopa	norepinephrine precursor	MSL	-0.01104	-0.03244	-0.04537	-0.02397	0.014847
K20468903	BNC105	tubulin polymerization inhibitor	MSL	-0.11193	-0.07446	-0.09188	-0.08585	-0.11348
K20722021	CEP-32496	RAF inhibitor	M	0.165552	0.198546	0.167139	-0.15151	0.146779
K20920669	cromoglicic-acid	immunosuppressant	IM	-0.09371	-0.06183	-0.05807	0.04114	-0.0649
K21071223	VP-20629	beta amyloid antagonist	IM	-0.05479	-0.10002	-0.08624	0.061572	-0.10992
K21077415	AMG-319	PI3K inhibitor	MSL	-0.0218	-0.00518	-0.07748	-0.12017	-0.04463
K21152241	enoximone	phosphodiesterase inhibitor	MSL	0.070904	0.018644	-0.02835	-0.04057	0.032338
K21191422	selexipag	platelet aggregation inhibitor; IP1 prostacyclin receptor agonist	MSL	-0.10716	-0.02894	-0.08401	0.003673	0.042186
K21237892	semapimod	cytokine production inhibitor; p38 MAPK inhibitor	MSL	0.012643	0.126689	-0.0812	-0.09225	0.207005
K21372554	cefetamet-pivoxil	bacterial cell wall synthesis inhibitor	IM	-0.12174	-0.01246	-0.041	0.001642	-0.06679
K21450440	benzthiazide	carbonic anhydrase inhibitor	M	0.065069	-0.0228	-0.07499	-0.00741	-0.08286
K21520694	sulfacetamide	PABA antagonist	IM	-0.02431	-0.07824	-0.05729	-0.02575	-0.02586
K21612934	leteprinim	nerve growth factor agonist	MSL	-0.08293	0.085753	-0.09795	-0.1262	0.025073
K21908111	AZD1208	Pim kinase inhibitor	M	0.034721	0.063589	0.004575	-0.02916	0.028679
K22134346	simvastatin	HMGCR inhibitor	M	0.067288	0.085057	-0.1054	-0.24598	0.0435
K22514639	EGF816	EGFR inhibitor	IM	-0.07885	-0.11656	0.293672	0.240042	0.015562
K22861715	chrysin	breast cancer resistance protein inhibitor	IM	-0.12997	-0.02384	0.062876	0.011338	0.032259
K23163214	dizocilpine-(-)	glutamate receptor antagonist	MSL	0.027285	-0.0703	-0.09183	-0.00928	-0.06945
K23190681	AV-412	protein tyrosine kinase inhibitor	IM	-0.09469	-0.16678	0.337777	0.231695	-0.04654
K23672206	BCI-540	glutamate receptor agonist	MSL	-0.02488	0.076892	-0.18145	-0.08152	0.012343
K23677682	voreloxin	topoisomerase inhibitor	MSL	-0.04486	0.029195	-0.06474	-0.09678	0.014952
K23925186	oridonin	BCL inhibitor	M	0.132126	0.205549	-0.13284	-0.29026	0.182341
K24187789	VU0238429	acetylcholine receptor allosteric modulator	M	-0.07773	0.044152	-0.15108	-0.18678	-0.02333
K24221957	pralidoxime-chloride	acetylcholinesterase inhibitor	MSL	0.007532	-0.08276	-0.01101	-0.02894	-0.13744

K24258499	vanillin		IM	-0.11856	-0.13911	0.098569	0.083791	-0.12984
K24443618	etebenecid	uricosuric blocker	IM	-0.07421	-0.00277	-0.03082	0.043708	0.052056
K24610819	amibegron	adrenergic receptor agonist	MSL	0.007642	0.087713	-0.15737	-0.07103	0.013476
K24666289	copanlisib	PI3K inhibitor	IM	-0.04959	-0.11897	0.384041	0.161827	-0.08326
K24820488	CH-170		MSL	0.034145	-0.08902	-0.09413	0.069434	-0.11906
K25186396	tangeritin	cell cycle inhibitor	IM	-0.09411	-0.06559	-0.06252	0.048909	-0.01838
K25204779	pritelivir	helicase primase inhibitor	IM	-0.14069	-0.00386	0.014593	-0.02645	-0.005
K25243230	oxytocin	oxytocin receptor agonist	MSL	0.041671	-0.06688	-0.03975	0.017894	-0.07667
K25494650	chlorproguanil	dihydrofolate reductase inhibitor	MSL	-0.04792	0.065011	-0.12459	-0.12927	0.038087
K25835157	PRT062070	JAK inhibitor; syk inhibitor	M	0.00956	0.130468	0.02542	-0.1204	0.09515
K25970317	resibufogenin	Na/K-ATPase inhibitor	MSL	-0.05263	-0.07748	-0.2401	-0.07864	-0.09203
K26168087	magnolol	PPAR receptor agonist	IM	-0.12924	-0.08293	0.002903	0.091225	-0.07745
K26222048	trans-10,cis-12-Conjugated-linoleic-acid		IM	-0.10091	-0.11382	0.00293	0.05243	-0.07628
K26530649	carboxypyridine-disulfide		MSL	-0.05161	0.001847	-0.11927	-0.07858	-0.02977
K26603252	PD-153035	EGFR inhibitor	IM	-0.12324	-0.15333	0.391061	0.290451	-0.03709
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	M	0.083765	0.302478	-0.07421	-0.30356	0.246345
K26838195	AST-1306	EGFR inhibitor	IM	-0.07988	-0.06985	0.298567	0.185083	0.043791
K27293958	tiaramide	anti-inflammatory agent	MSL	-0.01164	0.067585	-0.12292	-0.13766	0.018729
K27737647	H-89	PKA inhibitor	M	0.092753	-0.02458	-0.08057	-0.02505	-0.07686
K27799744	cyclovirobuxin-d	calcium channel modulator	M	0.067206	0.03318	0.046193	-0.04158	0.026665
K27911943	chromanol-293B-(-)-[3R,4S]	potassium channel blocker	IM	-0.08029	-0.09685	0.102101	0.087737	-0.09957
K27938825	ASA-404	angiogenesis inhibitor	MSL	0.079591	0.041909	-0.07013	-0.06289	0.008515
K28061410	beta-lapachone	topoisomerase inhibitor	M	0.121653	0.313665	-0.04815	-0.31661	0.182082
K28210218	cephalothin	bacterial cell wall synthesis inhibitor	MSL	0.045571	0.028234	-0.09175	-0.04328	-0.01503
K28217197	ganaxolone	GABA receptor modulator	IM	-0.089	-0.14842	0.124007	0.167991	-0.10835
K28405228	mecarbinate		IM	-0.07862	-0.08712	-0.08851	0.042383	-0.09259
K28537285	chidamide	HDAC inhibitor	MSL	-0.03251	0.020078	-0.01799	-0.05874	0.030949

K28687144	fosfosal	phosphodiesterase inhibitor	MSL	0.028863	0.007647	-0.05999	-0.05618	-0.01003
K28824103	genipin	choleretic agent	M	0.094785	0.144955	-0.1193	-0.21684	0.105229
K29133151	ICI-185,282	thromboxane receptor antagonist	IM	-0.09302	-0.05673	0.141827	0.071292	-0.02205
K29322660	edoxaban	coagulation factor inhibitor	IM	-0.15472	-0.06457	0.002997	0.057855	-0.04528
K29812331	dimemorfan	sigma receptor agonist	MSL	-0.08644	-0.05498	-0.0952	0.016349	-0.01506
K29895144	SKLB1002	VEGFR inhibitor	MSL	0.023841	0.014703	-0.05424	-0.00342	0.037882
K29905972	axitinib	PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	M	0.081599	0.070755	-0.02527	-0.11161	0.004812
K30159788	RSV604	RSV replication inhibitor	MSL	-0.0004	0.037533	-0.20377	-0.06521	0.050206
K30519779	homoquinolinic-acid	glutamate receptor agonist	IM	-0.11207	-0.08778	0.003236	0.056629	-0.0252
K30572193	CTEP	glutamate receptor antagonist	IM	-0.16455	-0.00044	0.088796	0.015499	0.000238
K30577245	docetaxel	tubulin polymerization inhibitor	IM	-0.13437	-0.12384	0.123481	0.068662	-0.10936
K30933884	UNBS-5162	CC chemokine receptor antagonist	M	0.098439	0.162311	-0.03433	-0.20286	0.091475
K30977212	PIK-293	PI3K inhibitor	IM	-0.13973	-0.06338	0.00947	0.066004	0.024673
K31283835	tofacitinib	JAK inhibitor	IM	-0.09231	-0.06137	-0.00174	0.012824	-0.07575
K31309378	lucitanib	FGFR inhibitor; VEGFR inhibitor	MSL	-0.05947	0.073952	-0.06451	-0.12232	0.00043
K31476763	AZD9668	elastase inhibitor	M	0.069343	0.067743	0.009005	-0.11388	-0.00254
K31495718	AZD7687	diacylglycerol O acyltransferase inhibitor	IM	-0.02143	-0.05809	0.08286	0.08898	-0.03167
K31698212	icotinib	EGFR inhibitor	IM	-0.13826	-0.26608	0.352891	0.310877	-0.10753
K31866293	TAK-632	RAF inhibitor	M	0.084888	0.304244	0.04709	-0.27088	0.20887
K31920458	mestranol	estrogen receptor agonist	IM	-0.07999	-0.00535	0.011648	0.007728	-0.05874
K32256160	solithromycin	protein synthesis inhibitor	MSL	0.033302	-0.13232	-0.07345	-0.0286	-0.14777
K32292990	CGP-53353	EGFR inhibitor; PKC inhibitor	IM	-0.10733	-0.03055	0.112914	-0.03902	0.019108
K32744045	disulfiram	aldehyde dehydrogenase inhibitor; DNA methyltransferase inhibitor; TRPV agonist	M	0.159232	0.146768	-0.07301	-0.08197	0.140484
K33425534	exemestane	aromatase inhibitor	M	0.030809	0.079207	-0.04525	-0.10564	0.03291
K33882852	ZK-93423	benzodiazepine receptor agonist	M	0.10975	0.206781	-0.01274	-0.14794	0.176686
K34328244	MF-101	estrogen receptor agonist	IM	-0.0589	-0.09967	0.051616	0.063156	-0.04255

K3441947	streptozotocin	DNA alkylating agent	MSL	0.036014	-0.07058	-0.07788	0.076155	-0.06131
K3444526l	SLV-320	adenosine receptor antagonist	MSL	0.085278	0.073939	-0.08758	-0.10739	0.082357
K3467290 3	HEMADO		IM	-0.08651	-0.0662	0.184852	0.057367	-0.09381
K3480193 0	AZD5069	CC chemokine receptor antagonist	IM	-0.151	-0.07882	0.028755	0.1362	-0.00725
K3487004 3	adoprazine	dopamine receptor antagonist, serotonin receptor agonist	M	0.041238	0.111176	0.045812	-0.08108	0.12551
K3536706 1	LY223982	leukotriene receptor antagonist	MSL	0.000351	0.013234	-0.01914	0.005739	-0.04973
K3619857 1	WAY-170523	metalloproteinase inhibitor	MSL	0.051599	-0.0044	-0.04718	-0.01887	0.02955
K3625887 7	AZ-10417808	caspase inhibitor	IM	-0.18391	-0.06367	0.258775	0.033406	-0.05539
K3627003 7	esculin	antioxidant	IM	-0.05207	-0.07189	0.102078	0.055975	-0.0386
K3638608 6	dolutegravir	HIV integrase inhibitor	M	0.116822	0.187969	-0.06818	-0.19967	0.141021
K3657412 7	LOXO-101	tropomyosin receptor kinase inhibitor	IM	-0.07758	-0.14625	0.151335	0.094925	-0.11517
K3688945 1	tetramethylthiuram-monosulfide		MSL	-0.05667	0.011406	-0.05004	-0.01495	-0.0223
K3696558 6	m-Chlorophenylbiguanide		IM	-0.09639	-0.14796	0.11287	0.086553	-0.0968
K3756185 7	zardaverine	phosphodiesterase inhibitor	M	0.178243	0.129869	-0.21466	-0.19572	0.169947
K3759025 7	GSK2560660	phosphodiesterase inhibitor	IM	-0.17817	-0.12278	0.068568	0.115542	-0.11693
K3770869 9	exisulind	phosphodiesterase inhibitor	MSL	0.007602	0.115747	-0.1137	-0.10746	0.086911
K3779849 9	etoposide	topoisomerase inhibitor	M	-0.03294	-0.00653	0.040224	-0.09649	-0.05532
K3814010 8	gadodiamide	radiopaque medium	IM	-0.11277	-0.07426	-0.03759	0.048857	-0.0433
K3816844 1	dabigatran	thrombin inhibitor	MSL	-0.0756	0.028068	-0.08152	-0.08549	-0.06551
K3838012 6	thiamet-g	GLCNAC phosphotransferase inhibitor	MSL	0.082065	-0.00247	-0.01406	-0.01394	0.003014
K3847399 8	cilomilast	phosphodiesterase inhibitor	IM	-0.10002	-0.03855	-0.16763	0.005967	-0.11845
K3900948 4	entrectinib	ALK tyrosine kinase receptor inhibitor; proto-oncogene tyrosine protein kinase inhibitor	IM	-0.2145	-0.09031	0.081441	0.076559	-0.03072
K3912059 5	bithionol	autotaxin inhibitor	IM	-0.13854	-0.07219	0.141648	0.099233	-0.03398
K3916652 8	ID-8		IM	-0.06014	-0.07214	0.071957	0.118755	-0.10241
K3937121 6	cyacetacide		MSL	0.037813	-0.19511	-0.02093	0.130175	-0.11905
K3962440 9	ADL5859	opioid receptor agonist	M	0.087985	0.038602	-0.06954	-0.10884	0.007408

K39974922	lenvatinib	FGFR inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	MSL	-0.03256	0.077346	-0.10886	-0.16946	0.002695
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	M	0.256196	0.247451	-0.01627	-0.19866	0.168251
K40654626	ditiocarb-sodium-trihydrate	immunostimulant	MSL	-0.01519	-0.07988	-0.01951	0.031028	-0.10956
K40718343	AEE788	EGFR inhibitor; VEGFR inhibitor	IM	-0.1022	-0.09967	0.382868	0.199126	0.018756
K40905133	phenacemide	sodium channel blocker	IM	-0.17177	-0.08373	-0.06578	0.065998	0.021264
K40992116	parachlorophenol	antiinfective drug	IM	-0.17449	-0.0181	-0.04431	-0.00932	0.016576
K41024817	4-phenolsulfonic-acid		IM	-0.15688	-0.06223	0.006866	0.027169	-0.03477
K41256143	dehydroepiandrosterone	protein synthesis stimulant	IM	-0.13521	-0.07818	-0.02423	0.066763	-0.06806
K41438959	perampanel	glutamate receptor antagonist	IM	-0.11441	-0.03076	0.110379	-0.00313	-0.02712
K41859756	NVP-AUY922	HSP inhibitor	IM	-0.17335	-0.03423	0.019695	-0.08198	-0.03736
K42090719	trichloroacetic-acid		IM	-0.0717	-0.04086	-0.02085	0.089242	0.060841
K42673188	verubulin	tubulin polymerization inhibitor	MSL	-0.09012	-0.03568	-0.01487	-0.06849	-0.05141
K42805893	osimertinib	EGFR inhibitor	IM	-0.06781	-0.05978	0.377375	0.229006	0.075302
K42981054	mibampator	glutamate receptor modulator	M	0.097536	0.001457	0.112583	-0.03964	0.042554
K42991124	creatinol-phosphate		IM	-0.08518	-0.00785	-0.06276	0.001052	0.027575
K43410529	MLN2480	RAF inhibitor	M	0.0501	0.184598	0.00079	-0.19661	0.197592
K43890836	gemcadiol	antilipemic	MSL	-0.0826	-0.17678	-0.01587	0.033766	-0.17307
K44164034	pumosetrag	serotonin receptor agonist	MSL	-0.05227	-0.09804	-0.13909	0.052217	-0.0985
K44590731	TU-2100		IM	-0.04996	-0.09456	0.055172	0.032532	-0.0627
K44777625	FH1	hepatocyte function enhancer	IM	-0.08253	-0.10997	-0.14259	0.012367	-0.06073
K44974079	ticagrelor	purinergic receptor antagonist	MSL	0.023118	-0.03833	-0.07713	-0.06078	0.012863
K45014108	ephedrine	adrenergic receptor agonist	IM	-0.10993	-0.03098	-0.05617	0.037011	-0.08521
K45033733	famciclovir	DNA polymerase inhibitor	IM	-0.13195	-0.06777	-0.01906	0.054406	-0.08807
K45114938	mezlocillin	bacterial cell wall synthesis inhibitor	IM	-0.07537	-0.03356	-0.09296	0.006699	-0.03457
K45125084	zolimidine	mucus protecting agent	M	0.132957	0.03578	-0.09035	-0.07228	0.058752
K45168550	SB-756050	G protein-coupled receptor agonist	IM	-0.07957	-0.03347	0.015771	-0.03952	-0.06711
K45293975	7-hydroxystaurosporine	CDK inhibitor; CHK inhibitor; PKC inhibitor	IM	-0.15153	-0.06588	0.090881	0.06924	-0.07646

K45437867	5-methylfurmethiodide	acetylcholine receptor agonist	IM	-0.14129	-0.09845	0.084403	0.067827	-0.01347
K45519571	RN-1747	TRPV agonist	IM	-0.18391	-0.14405	0.126911	0.142784	-0.09773
K45724504	anguidine	protein synthesis inhibitor	IM	-0.16382	-0.1066	0.208315	0.097134	-0.12405
K45906612	presatovir	RSV fusion inhibitor	MSL	0.003391	0.08224	-0.04286	0.010238	-0.00362
K45916615	danofloxacin	bacterial DNA gyrase inhibitor	IM	-0.09057	-0.01362	-0.03133	-0.03681	-0.01901
K46386702	ARRY-334543	EGFR inhibitor	IM	-0.05992	-0.1679	0.362184	0.263188	-0.03109
K46625559	ozanimod	sphingosine 1 phosphate receptor agonist	MSL	-0.06933	-0.01467	-0.1062	0.008869	-0.00325
K47079459	cetrimonium		IM	-0.07274	-0.04223	0.062435	0.064439	-0.01557
K47150025	KI-8751	KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	M	0.025124	0.103896	0.006054	-0.09761	0.037321
K47554101	eperezolid	bacterial 30S ribosomal subunit inhibitor	IM	-0.07798	-0.0187	-0.09524	-0.02493	-0.04423
K47598052	PP-1	src inhibitor	IM	-0.15774	-0.05172	0.117537	0.052592	-0.12268
K47929404	vercirnon	CC chemokine receptor antagonist	MSL	-0.01789	0.03409	-0.13167	-0.07744	-0.04665
K48068743	teneligliptin	dipeptidyl peptidase inhibitor	IM	-0.10057	-0.10714	-0.06979	0.048309	-0.12459
K48443249	CNX-774	Bruton's tyrosine kinase (BTK) inhibitor	M	0.078022	0.093581	0.024629	-0.09506	0.138921
K48452630	SRT2104	SIRT activator	MSL	-0.07665	-0.05657	-0.08685	0.069648	-0.05596
K48830578	OMDM-2	FAAH inhibitor	MSL	0.00432	0.078566	-0.10684	-0.13149	0.088637
K49075727	nintedanib	FGFR inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	MSL	-0.04785	0.16111	-0.09244	-0.17045	0.134821
K49294207	BIBU-1361	EGFR inhibitor	IM	-0.06618	-0.1599	0.47829	0.251671	-0.00947
K49313711	ribitol		IM	-0.06938	-0.06045	0.062396	0.082565	-0.04956
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	IM	-0.17261	-0.14603	0.113298	0.097507	-0.06188
K49371609	PIK-75	DNA protein kinase inhibitor; PI3K inhibitor	IM	-0.11777	-0.15406	0.077057	0.127026	-0.16957
K49481516	galantamine	acetylcholinesterase inhibitor	IM	-0.148	-0.19516	0.065157	0.09079	-0.20144
K49669041	BX-912	pyruvate dehydrogenase kinase inhibitor	M	0.04083	0.154246	-0.03732	-0.23675	0.035229
K50010139	poziotinib	EGFR inhibitor	IM	-0.16686	-0.12615	0.344706	0.216384	-0.02553
K50050533	docosanol	lipase clearing factor inhibitor	IM	-0.06288	-0.0995	-0.04968	0.094732	-0.06037
K50293352	MM77	serotonin receptor antagonist	IM	-0.12411	-0.07111	0.009431	0.078062	-0.06165

K50325075	UCL-2077	slow afterhyperpolarization channel blocker	IM	-0.20055	-0.10508	0.11276	0.087806	-0.07511
K50388907	fenofibrate	PPAR receptor agonist	IM	-0.11683	-0.14399	0.285186	0.231846	-0.03064
K50417881	eticlopride	dopamine receptor antagonist	IM	-0.07879	-0.03475	-0.14196	-0.02344	-0.03396
K51541829	Ro-25-6981		IM	-0.07012	-0.15131	-0.0147	0.047075	-0.12466
K51671335	levosulpiride	dopamine receptor antagonist	MSL	0.107658	-0.11408	-0.00136	0.12286	-0.12095
K51747290	hydroxyurea	ribonucleotide reductase inhibitor	IM	-0.10487	-0.06108	-0.03196	0.047566	-0.05508
K51751936	alfadolone-acetate	benzodiazepine receptor agonist	IM	-0.12963	-0.07327	0.026722	0.070515	-0.04454
K51770398	JNJ-17203212	TRPV antagonist	IM	-0.10372	-0.03139	0.141985	0.036549	-0.00666
K51784806	alacepril	angiotensin converting enzyme inhibitor	M	0.004384	0.13897	-0.19551	-0.13404	0.154141
K52020312	metronidazole	DNA inhibitor	IM	-0.15233	-0.08969	0.053225	0.030201	-0.06039
K52256627	chlorhexidine	membrane integrity inhibitor	M	0.14564	0.166455	-0.11132	-0.15937	0.086625
K52408781	clobazam	GABA benzodiazepine site receptor agonist	IM	-0.10318	-0.08124	0.087132	0.051505	-0.07058
K52914072	LTA		MSL	0.001953	-0.02051	-0.06874	-0.04386	0.014603
K53097745	pterostilbene	cyclooxygenase inhibitor, PPAR receptor agonist	MSL	-0.0588	-0.08513	-0.05713	0.060629	-0.06647
K53156626	7-methoxytacrine	acetylcholinesterase inhibitor	MSL	-0.03204	-0.03879	-0.06604	-0.03683	0.06329
K53195974	sipatrigine	voltage-gated sodium channel blocker	IM	-0.13153	-0.00213	0.076823	-0.01806	0.012277
K53205568	afalanine	dopamine receptor agonist	IM	-0.12942	-0.16637	0.063889	0.157833	-0.06352
K53236343	aprindine	voltage-gated sodium channel blocker	M	0.005508	0.076781	-0.10961	-0.10894	0.067142
K53581288	baricitinib	JAK inhibitor	IM	-0.15406	-0.04059	-0.08102	0.059694	-0.0321
K53809807	fosphenytoin	sodium channel blocker	MSL	0.008138	-0.11284	-0.13291	0.000687	-0.10855
K53814070	ripasudil	rho associated kinase inhibitor	MSL	-0.1492	-0.06374	-0.14823	-0.06435	-0.05247
K53857191	risperidone	dopamine receptor antagonist; serotonin receptor antagonist	MSL	-0.06307	-0.11173	-0.14329	0.013526	-0.11209
K53963539	vortioxetine	serotonin receptor agonist; serotonin receptor antagonist	IM	-0.12603	-0.01414	-0.01638	-0.02013	0.010164
K54247840	halofuginone	collagenase inhibitor	IM	-0.14225	-0.08061	0.060211	0.044536	-0.04258
K54256913	MK-1775	WEE1 kinase inhibitor	IM	-0.09981	-0.18779	0.117528	0.165509	-0.15373
K54339150	proquazone	cyclooxygenase inhibitor	MSL	0.009492	0.020664	-0.07792	-0.09809	0.020307
K54395039	PR-619	DUB inhibitor	M	0.099296	0.149535	-0.12228	-0.22033	0.056745

K54634444	artesunate	DNA synthesis inhibitor	M	0.132469	0.157504	0.046551	-0.17875	0.077482
K54770957	etoricoxib	cyclooxygenase inhibitor	IM	-0.1183	-0.12895	0.02269	0.123329	-0.06605
K54955827	niraparib	PARP inhibitor	M	0.035768	-0.02358	-0.10001	-0.10909	-0.03477
K54997624	alpelisib	PI3K inhibitor	IM	-0.08851	-0.04958	0.216096	0.138375	0.020615
K55172746	apricitabine	nucleoside reverse transcriptase inhibitor	MSL	0.02836	0.026506	-0.08862	-0.10951	-0.04005
K55696337	topotecan	topoisomerase inhibitor	IM	-0.16199	-0.03228	0.07572	-0.0378	-0.05843
K55705469	penbutolol	adrenergic receptor antagonist	M	0.039307	0.077353	-0.07801	-0.07482	0.017902
K56032964	AP26113	ALK tyrosine kinase receptor inhibitor	IM	-0.11487	-0.10102	0.191859	0.114139	-0.04914
K56211775	RTA-408	nitric oxide production inhibitor	IM	-0.14048	-0.06968	0.083236	0.017447	-0.04828
K56277358	MGCD-265	VEGFR inhibitor	MSL	-0.05784	0.100077	-0.0439	-0.07228	0.080488
K56405753	MK-2461	FGFR inhibitor; VEGFR inhibitor	MSL	-0.03035	0.05424	-0.01237	-0.12881	-0.00757
K56483981	chicago-sky-blue-6b	glutamate inhibitor; macrophage migration inhibiting factor inhibitor	IM	-0.1611	-0.17007	0.18405	0.159884	-0.07521
K56614220	clofazimine	GK0582 inhibitor	M	0.14707	0.152968	0.085301	-0.09284	0.106905
K56707426	nitarsone		MSL	0.033888	-0.01836	-0.02358	0.023462	-0.04129
K56751279	Y-39983	rho associated kinase inhibitor	M	-0.00611	0.056164	-0.17608	-0.10224	-0.02374
K56912469	SAR407899	rho associated kinase inhibitor	MSL	0.076732	0.003595	-0.22773	-0.10519	-0.00558
K56957086	dacinostat	HDAC inhibitor	IM	-0.1602	-0.07883	0.10812	0.061513	-0.1024
K56981171	brigatinib	ALK tyrosine kinase receptor inhibitor; EGFR inhibitor	IM	-0.17279	-0.04068	0.119946	0.027015	0.040238
K57169635	dacomitinib	EGFR inhibitor	IM	-0.11009	-0.07724	0.376362	0.196894	0.022339
K57427145	ripazepam	benzodiazepine receptor agonist	MSL	0.073026	-0.09455	-0.0411	0.050636	-0.07501
K58466253	palmatine-chloride	dopamine synthesis inhibitor	M	0.191556	0.117239	-0.12098	-0.16452	0.060979
K58501140	TAK-875	insulin secretagogue	MSL	0.031822	0.00946	-0.00217	-0.00346	-0.03291
K58529924	ONC201	AKT inhibitor; MAP kinase inhibitor	M	0.050772	0.147903	-0.10747	-0.18719	0.104631
K59256312	gabexate	serine protease inhibitor	M	0.004068	0.006432	-0.1971	-0.03992	-0.01776
K59436580	tedizolid	bacterial 50S ribosomal subunit inhibitor	M	0.115866	0.163451	-0.01192	-0.09248	0.137835
K59753975	vindesine	tubulin polymerization inhibitor	MSL	-0.099	-0.05229	-0.07282	-0.10853	-0.11151
K60038276	irbesartan	angiotensin receptor antagonist	IM	-0.12978	-0.05717	-0.06191	0.024934	-0.11703

K60130390	UNC0642	histone lysine methyltransferase inhibitor	IM	-0.0704	-0.20493	0.178865	0.145585	-0.1219
K60230970	MG-132	proteasome inhibitor	IM	-0.16705	-0.02075	0.021603	0.015206	0.047125
K60237333	niacin	NAD precursor; vitamin B	IM	-0.09449	-0.02672	-0.01502	-0.01548	0.025392
K60241851	isodibut	aldehyde reductase inhibitor	MSL	0.050746	-0.04572	-0.10394	-0.03436	-0.0652
K60369935	ribavirin	antiviral	M	0.116243	0.115464	-0.0009	-0.03039	0.084068
K60443845	chlormidazole	fungal lanosterol demethylase inhibitor	M	0.20157	0.174446	-0.00691	-0.16596	0.161226
K61097567	SB-218795	tachykinin antagonist	IM	-0.13767	-0.01019	-0.10474	0.017786	-0.06114
K61279411	oxaloacetate	glutamate release inhibitor	IM	-0.09347	-0.03375	-0.12458	0.040808	-0.00273
K61337602	naratriptan	serotonin receptor agonist	IM	-0.11416	-0.05093	0.027761	-0.00581	0.051605
K61443650	thiomersal	other antibiotic	M	-0.05708	0.141662	-0.12375	-0.2551	0.028697
K61688984	RGFP966	HDAC inhibitor	MSL	0.069122	-0.101	-0.02113	-0.03962	-0.02541
K61717546	fleroxacin	topoisomerase inhibitor	IM	-0.06537	-0.08463	0.033342	0.067758	-0.09069
K62200014	anagrelide	phosphodiesterase inhibitor	M	0.152247	0.223472	-0.1054	-0.19312	0.254063
K62213621	dihydroartemisinin	antimalarial agent	M	0.185453	0.164342	0.016492	-0.17576	0.134506
K62374002	PI3K-IN-2	PI3K inhibitor	IM	-0.07052	-0.0386	0.201271	0.078617	0.01769
K62412084	para-toluenesulfonamide		IM	-0.08582	-0.03201	-0.02125	0.030771	0.031819
K62427771	AS-77	potassium channel blocker	MSL	-0.00922	-0.01368	-0.04012	-0.04584	0.049708
K63150726	JTE-907	cannabinoid receptor inverse agonist	IM	-0.13101	-0.05167	-0.01924	0.087247	-0.04389
K63630713	etacrynic-acid	sodium/potassium/chloride transporter inhibitor	IM	-0.15224	-0.00582	0.025267	-0.04481	0.02339
K63712959	temoporfin	radical formation stimulant	M	-0.028	0.01902	-0.13406	-0.04512	0.030397
K63932022	2'-MeCCPA	adenosine receptor agonist	MSL	-0.01341	-0.06271	-0.04413	0.034523	-0.0753
K64052750	gefitinib	EGFR inhibitor	IM	-0.06642	-0.18805	0.441103	0.312071	-0.05639
K64120610	vinflunine	microtubule inhibitor	M	-0.04762	-0.03782	0.039019	-0.042	-0.03707
K64755930	etazolate	phosphodiesterase inhibitor	IM	-0.13298	-0.13051	-0.09327	0.031045	-0.20601
K64835161	ML167	CLK inhibitor; DYRK inhibitor	IM	-0.07536	-0.07672	0.017805	0.058357	-0.03284
K64888243	AZ960	JAK inhibitor	IM	-0.13497	-0.0625	0.055087	0.008122	-0.07766
K65498798	abametapir	metalloproteinase inhibitor	MSL	0.033789	-0.04148	-0.12308	-0.00257	-0.09619

K65856711	rolipram-S(+)	phosphodiesterase inhibitor	IM	-0.10432	-0.03939	-0.06426	-0.06383	-0.07222
K65900713	caroverine	glutamate receptor antagonist; calcium channel blocker	MSL	0.05539	-0.0572	-0.10428	0.001324	-0.01545
K66094457	CPP	glutamate receptor antagonist	MSL	-0.04563	-0.04467	-0.2411	-0.01154	-0.04842
K66175015	afatinib	EGFR inhibitor	IM	-0.10367	-0.04742	0.314961	0.144973	0.061442
K66296774	fluvastatin	HMGCR inhibitor	M	-0.06321	-0.12209	0.040377	-0.05653	-0.10262
K66437909	KT-433	uricosuric agent	MSL	-0.07552	-0.02445	-0.06092	-0.01366	0.017374
K66538826	amuvatinib	FLT3 inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; RAD51 inhibitor; RET tyrosine kinase inhibitor	M	0.135714	0.143845	0.028057	-0.07438	0.115285
K66715657	UH-232-(+)	dopamine receptor antagonist	IM	-0.08225	-0.10064	0.116886	0.08495	-0.11458
K66808046	oxyquinoline	chelating agent	M	0.117824	0.175696	-0.04854	-0.16134	0.135313
K66845263	sophocarpine		MSL	-0.0048	-0.09778	-0.09949	0.02582	-0.08854
K67173685	4E1RCat	protein synthesis inhibitor	M	0.15508	0.055641	0.010513	-0.08971	0.016269
K67217586	fenthion	cholinesterase inhibitor	M	0.012324	0.012906	0.026896	-0.06781	0.055719
K67578145	GDC-0879	RAF inhibitor	M	0.110094	0.209026	0.112872	-0.18739	0.15809
K67783091	haloperidol	dopamine receptor antagonist	IM	-0.11242	-0.11265	0.102477	0.035997	-0.1016
K68336408	tyrphostin-AG-1478	EGFR inhibitor	IM	-0.0761	-0.09525	0.343383	0.225881	0.028937
K68408772	carboxyamidotriazole	calcium channel blocker	M	0.111446	0.135875	-0.06044	-0.08683	0.145825
K68432770	ampicillin	bacterial cell wall synthesis inhibitor	MSL	0.02394	-0.05408	-0.09834	-0.05206	-0.06314
K68488863	ENMD-2076	Aurora kinase inhibitor; FLT3 inhibitor; VEGFR inhibitor	MSL	-0.05611	0.02617	-0.02079	-0.10569	-0.05051
K68553471	todralazine	antihypertensive agent	IM	-0.0824	-0.10389	0.045407	0.054547	-0.08124
K68747584	PF-03814735	Aurora kinase inhibitor	MSL	-0.01193	0.015965	-0.04366	-0.07539	-0.05974
K68764924	pantethine	coenzyme A precursor	IM	-0.12373	-0.02138	0.120562	0.041295	-0.01343
K69726342	atorvastatin	HMGCR inhibitor	M	0.115334	0.105687	-0.09939	-0.24151	0.076984
K69907333	flurbiprofen-(S)-(+)	cyclooxygenase inhibitor	IM	-0.04195	-0.0194	0.029424	0.018893	-0.0319
K70301465	ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor	IM	-0.0828	-0.09233	0.406517	0.23678	0.022855
K70487031	flupentixol	dopamine receptor antagonist	IM	-0.10409	-0.05449	0.153586	0.108568	-0.04775
K70792160	10-DEBC	AKT inhibitor	IM	-0.11088	-0.00116	-0.03074	-0.0627	-0.02503

K70914287	BIBX-1382	EGFR inhibitor	IM	-0.03277	-0.19997	0.312955	0.250931	-0.07259
K71075609	dorzolamide	carbonic anhydrase inhibitor	M	0.071234	0.04159	-0.08131	-0.09409	0.011006
K71499074	diclofenamide	carbonic anhydrase inhibitor	MSL	-0.07682	-0.13011	-0.00564	0.060824	-0.13556
K71534238	GW-9508	free fatty acid receptor agonist; G protein-coupled receptor agonist	MSL	-0.03704	-0.0358	-0.05526	0.060629	-0.04742
K71926323	marbofloxacin	bacterial DNA gyrase inhibitor	IM	-0.15249	-0.03736	-0.00807	-0.00013	-0.03718
K72106461	SYM-2081	kainate receptor antagonist	IM	-0.0674	-0.08842	0.05746	0.016031	-0.13111
K72280606	gilteritinib	FLT3 inhibitor	IM	-0.14704	-0.04581	0.074562	-0.01504	-0.01768
K72327355	baicalein	lipoxygenase inhibitor	IM	-0.14417	-0.06026	-0.04061	0.01721	-0.04244
K72414522	AZD5438	CDK inhibitor	IM	-0.08372	-0.14978	0.127056	0.084401	-0.13006
K72420232	WZ-4002	EGFR inhibitor	IM	-0.07257	-0.1059	0.350678	0.190731	0.017693
K72533376	etoposide-phosphate	topoisomerase inhibitor	MSL	-0.06661	0.124703	-0.0333	-0.17294	0.097081
K72723676	benzethonium	sodium channel blocker	M	0.156786	0.279522	0.104147	-0.21902	0.160433
K72951360	valrubicin	DNA inhibitor; topoisomerase inhibitor	M	-0.00301	0.032336	0.082401	-0.06157	0.010033
K73027814	oxyfedrine	adrenergic receptor agonist	MSL	0.007583	-0.06224	-0.05029	0.063575	-0.04763
K73132780	pyronaridine	antimalarial agent	IM	-0.18189	-0.18746	0.170042	0.244639	-0.13683
K73191876	alizarin		IM	-0.16152	-0.20251	-0.00609	0.195884	-0.23062
K73309154	OSI-420	EGFR inhibitor	IM	-0.11853	-0.01776	0.302701	0.141574	0.118421
K73319509	PF-04217903	c-Met inhibitor	IM	-0.11626	-0.04418	0.077708	0.074022	-0.00139
K73383190	C646	histone acetyltransferase inhibitor	MSL	0.102993	0.094869	-0.10324	-0.09473	0.060774
K73391359	dimethisoquin	local anesthetic	IM	-0.10101	-0.05619	-0.12637	-0.0517	-0.0274
K73585091	GS-9620	toll-like receptor agonist	MSL	0.002305	0.009784	-0.15048	-0.09554	-0.01739
K73753850	hexaminolevulinate		IM	-0.09428	-0.23539	0.182628	0.133368	-0.24324
K73838513	cinacalcet	calcium channel activator	IM	-0.10749	-0.06837	0.018741	0.004349	-0.00144
K73881242	arbidol	cytochrome P450 inhibitor	IM	-0.19755	-0.05354	0.049005	0.080456	0.002591
K74671368	idronoxil	XIAP inhibitor	MSL	-0.05796	0.071135	-0.14246	-0.22197	0.039836
K74913225	brinzolamide	carbonic anhydrase inhibitor	IM	-0.15267	-0.08625	0.001342	0.017103	-0.00363
K75080769	trans-4-[8-(3-Fluorophenyl)-1,7-naphthyridin-6-yl]cyclohexanecarboxylic-acid		IM	-0.1254	-0.10859	0.041206	0.089407	-0.09561

K75615183	talipexole	adrenergic receptor agonist; dopamine receptor agonist	M	0.061351	-0.01427	0.058603	-0.03535	-0.08717
K75855670	iodoquinol	antiseptic	MSL	-0.06766	0.03942	-0.10403	-0.09894	0.031627
K75958547	pitavastatin	HMGCR inhibitor	MSL	-0.04476	-0.08119	-0.0845	-0.1438	-0.0837
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	IM	-0.16658	-0.16482	0.346557	0.248551	0.013462
K76315403	cetrorelix	gonadotropin releasing factor hormone receptor antagonist	MSL	0.037232	-0.18278	-0.07051	-0.05533	-0.13444
K76614248	atizoram	phosphodiesterase inhibitor	MSL	-0.04268	-0.0276	-0.09365	0.012063	0.000749
K77484724	adefovir	DNA polymerase inhibitor	IM	-0.05371	-0.05487	-0.00969	-0.00707	-0.06705
K77561571	topiroxostat	xanthine oxidase inhibitor	MSL	-0.06728	-0.14463	-0.01359	0.086231	-0.19563
K77597856	detomidine	adrenergic receptor agonist	IM	-0.10768	-0.13783	0.074267	0.083014	-0.09938
K77625799	vandetanib	EGFR inhibitor; RET tyrosine kinase inhibitor; VEGFR inhibitor	IM	-0.11628	-0.04602	0.296134	0.120843	0.049274
K77627880	A205804	ICAM1 expression inhibitor	IM	-0.12732	-0.15624	0.073913	0.165468	-0.12354
K77641333	naphazoline	adrenergic receptor agonist	IM	-0.11467	-0.08753	0.035076	0.04142	-0.00742
K77685957	dequalinium	PKC inhibitor	M	0.183809	-0.00828	0.087084	-0.03298	0.003922
K77771411	moxonidine	imidazoline receptor agonist	IM	-0.08951	-0.21276	0.08201	0.139686	-0.26098
K77791657	3-deazaneplanocin-A	histone lysine methyltransferase inhibitor	IM	-0.1309	-0.02722	0.090339	0.150724	-0.05245
K78055238	LY2090314	glycogen synthase kinase inhibitor	MSL	-0.08353	-0.01913	-0.00714	0.041704	0.003829
K78096648	oxiperomide	dopamine receptor antagonist	M	0.16608	0.150247	-0.19984	-0.19632	0.085408
K78126613	menadione	mitochondrial DNA polymerase inhibitor; phosphatase inhibitor	M	0.004833	0.157516	-0.05102	-0.20537	0.116528
K78299798	mepiroxol		IM	-0.10818	-0.07855	0.017892	0.0253	-0.08258
K78567475	dolastatin-10	tubulin polymerization inhibitor	MSL	-0.07579	-0.05477	-0.00011	0.003299	-0.08086
K78666826	procaterol	adrenergic receptor agonist	IM	-0.19402	-0.22022	0.080601	0.133962	-0.1159
K79277568	methoxyamine	DNA repair enzyme inhibitor	IM	-0.05272	-0.10687	-0.03117	0.066224	-0.08534
K79710622	GKT137831	NADPH oxidase inhibitor	MSL	-0.01941	-0.01213	-0.12349	-0.11556	0.027049
K79821389	nibitecan	topoisomerase inhibitor	IM	-0.11776	-0.08132	0.164589	0.071206	-0.06417
K80043866	sodium-gualenate	antacid	IM	-0.0463	-0.12519	-0.00503	0.05288	-0.07597
K80343549	TAK-285	EGFR inhibitor	IM	-0.07158	-0.15978	0.178479	0.222079	-0.06872

K80353807	khellin	vasodilator	MSL	-0.05154	-0.06807	-0.14627	-0.06911	-0.10492
K80359953	talampanel	glutamate receptor antagonist	MSL	-0.00653	-0.02993	-0.00771	-0.03271	-0.04869
K80419150	debrisoquin	adrenergic neuron blocker	MSL	0.049189	-0.09369	-0.11534	-0.05638	-0.10054
K80480517	repsox	TGF beta receptor inhibitor	IM	-0.05665	-0.07924	0.08697	0.106197	-0.03254
K81016934	INC-280	c-Met inhibitor	IM	-0.13375	-0.08364	-0.03988	0.12875	0.005689
K81136890	leucylleucine-methyl-ester		IM	-0.10897	-0.1343	0.017746	0.040373	-0.18094
K81330143	tideglusib	glycogen synthase kinase inhibitor	M	0.169265	-0.00301	-0.17514	-0.01784	-0.03539
K81332461	maxacalcitol	vitamin D receptor agonist	IM	-0.07504	-0.07576	0.200324	0.130705	-0.00506
K81473089	tacrine	acetylcholinesterase inhibitor	IM	-0.14634	-0.01549	0.062641	0.03587	0.070795
K81548480	AC-264613	PAR agonist	IM	-0.07682	-0.07621	0.002402	0.093802	-0.03521
K81645907	captamine		IM	-0.14238	-0.0391	-0.05026	0.012321	-0.0463
K81672972	dinoprost	prostacyclin analog	IM	-0.06707	-0.08325	-0.07463	0.036073	-0.02378
K81728688	WZ8040	EGFR inhibitor	IM	-0.13869	-0.07504	0.289497	0.180539	0.042302
K81801188	PP-121	protein tyrosine kinase inhibitor	IM	-0.12182	-0.08606	0.02379	0.078213	-0.08787
K81807412	N6-methyladenosine		IM	-0.11803	-0.10798	-0.05829	0.022165	-0.08779
K82028950	CGH2466	adenosine receptor antagonist	IM	-0.09319	-0.07415	0.043309	0.037758	-0.01803
K82928847	ACY-1215	HDAC inhibitor	M	0.094251	0.158679	0.050582	-0.11818	0.218163
K82960980	ceftiofur	bacterial cell wall synthesis inhibitor	IM	-0.07342	-0.06755	0.082893	0.04597	-0.06957
K82967685	mirodenafil	phosphodiesterase inhibitor	MSL	-0.05009	-0.05595	-0.11332	0.072489	-0.05943
K83144676	olmesartan	angiotensin receptor antagonist	IM	-0.20014	-0.04767	-0.02847	0.018055	-0.0502
K83257731	chloropyramine	histamine receptor antagonist	M	-0.0016	0.120983	-0.05886	-0.17825	0.083052
K83776863	tryptophan	serotonin receptor partial agonist	M	0.044023	-0.06657	-0.06507	-0.01791	-0.09035
K84011460	nizofenone	ion channel antagonist	IM	-0.14245	-0.10603	0.033316	0.049138	-0.03805
K84810405	almorexant	orexin receptor antagonist	IM	-0.14273	-0.02075	0.025983	-0.02213	-0.02039
K84868168	erdafitinib	FGFR inhibitor	MSL	-0.0744	0.048316	-0.15447	-0.18637	0.006092
K85046107	ramosetron	serotonin receptor antagonist	IM	-0.1044	-0.2143	0.123416	0.165677	-0.22649
K85402309	dovitinib	EGFR inhibitor; FGFR inhibitor; FLT3 inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	M	-0.00848	0.022962	-0.0224	-0.09759	-0.0508

K86171477	eltoprazine	serotonin receptor agonist	IM	-0.05317	-0.00439	-0.07472	-0.08297	-0.0033
K86204871	terconazole	sterol demethylase inhibitor	IM	-0.11013	-0.13134	-0.03559	0.082447	-0.15851
K86307448	allopurinol	xanthine oxidase inhibitor	IM	-0.1123	-0.05119	0.037473	0.067675	0.002066
K86856088	UNC0638	histone lysine methyltransferase inhibitor	IM	-0.07586	-0.12643	0.169672	0.133158	-0.08839
K86882815	cabergoline	dopamine receptor agonist	IM	-0.10406	-0.0254	-0.00766	0.012508	0.071812
K87036601	azodicarbonamide	DNA synthesis inhibitor	IM	-0.08702	-0.05349	0.0555	0.03283	-0.07574
K87316765	prinaberel	estrogen receptor agonist	MSL	-0.00721	0.004934	-0.11333	-0.04804	0.029147
K87349682	norepinephrine	adrenergic receptor agonist	IM	-0.1184	-0.08076	0.105905	-0.01391	-0.05347
K87737963	cyt387		MSL	-0.03421	0.067632	-0.14158	-0.11421	0.000569
K88061624	mizoribine	immunosuppressant; inosine monophosphate dehydrogenase inhibitor	M	0.005053	-0.05786	0.073386	-0.00258	-0.02577
K88429204	pyrimethamine	dihydrofolate reductase inhibitor	MSL	0.085979	0.272942	-0.01069	-0.1849	0.28398
K88506063	KD025	rho associated kinase inhibitor	MSL	0.057163	-0.01081	-0.02606	-0.10459	-0.00306
K88544581	CI-976	ACAT inhibitor	MSL	0.091976	0.060823	-0.03363	-0.082	0.03532
K88807631	elacridar	P glycoprotein inhibitor	IM	-0.11012	-0.09531	0.081367	0.121247	-0.08896
K89053832	VLX600	ubiquitin C-terminal hydrolase inhibitor	IM	-0.21353	-0.12445	0.113456	0.061139	-0.12764
K89208535	indacaterol	adrenergic receptor agonist	IM	-0.1532	-0.09336	0.120724	0.05954	-0.08427
K89299012	DCEBIO	potassium channel activator	M	0.157728	0.120658	-0.1352	-0.11985	0.120994
K89413285	remimazolam	benzodiazepine receptor agonist	MSL	-0.02892	0.037853	-0.10586	-0.0431	-0.03395
K89634775	allylthiourea	nitrification inhibitor	IM	-0.13254	-0.04074	-0.08637	0.003499	-0.0553
K89704198	vincamine	adrenergic receptor antagonist	IM	-0.06329	-0.17047	-0.044	0.137068	-0.17673
K90239174	AMG-487	CC chemokine receptor antagonist	IM	-0.0821	-0.08583	0.15574	0.047664	-0.01666
K90825648	RS-127445	serotonin receptor antagonist	MSL	0.054312	0.053938	-0.05973	-0.12961	0.0427
K91758890	4-HQN	PARP inhibitor	IM	-0.14748	-0.06704	0.106286	0.04595	0.05447
K91825936	ZK811752	CC chemokine receptor antagonist	M	0.099526	0.109527	-0.00448	-0.08132	0.042807
K91868854	2-[1-(4-piperonyl)piperazinyl]benzothiazole	serotonin receptor agonist	MSL	0.00776	0.03417	-0.05087	-0.06017	0.011505
K92107055	pimecrolimus	calcineurin inhibitor	MSL	-0.01575	0.080851	-0.01742	-0.02862	0.077442

K92426617	esaprazole		IM	-0.05509	-0.03721	-0.02482	-0.04024	-0.09876
K92908289	medica-16	ATP citrase lyase inhibitor	MSL	-0.05017	-0.06152	-0.10856	0.016127	0.004343
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	M	0.101093	0.240203	-0.10449	-0.26903	0.191571
K93231391	ethambutol	bacterial cell wall synthesis inhibitor	IM	-0.10826	-0.12304	-0.02031	0.10026	-0.12796
K93240442	dinitolmide		IM	-0.13801	-0.07208	0.11087	0.035794	-0.07534
K93632104	sodium-salicylate	prostanoid receptor antagonist	M	0.033842	0.036068	0.025363	-0.02759	-0.02882
K94072573	medronic-acid	bone resorption inhibitor	MSL	0.072827	-0.13987	-0.16332	0.024658	-0.18716
K94176593	TWS-119	glycogen synthase kinase inhibitor	IM	-0.16057	-0.02666	0.133541	0.00573	-0.03964
K94239562	paeonol	anti-inflammatory agent	IM	-0.15024	-0.06775	-0.03331	0.070898	-0.06165
K94441233	mevastatin	HMGCR inhibitor	MSL	-0.00119	-0.07411	-0.15027	-0.13048	-0.09323
K94455792	ICG-001	beta-catenin inhibitor	M	0.178329	0.141485	0.019291	-0.22229	0.163484
K94832621	Y-134	estrogen receptor antagonist	IM	-0.11641	-0.12575	-0.04772	0.098443	-0.09333
K95260951	asenapine	dopamine receptor antagonist; serotonin receptor antagonist	MSL	-0.0115	0.067082	-0.17893	-0.19572	0.033668
K95309561	dienestrol	estrogen receptor agonist	IM	-0.10994	-0.05691	-0.0417	0.049847	-0.02711
K95523387	OLDA	TRPV agonist	MSL	0.095843	0.0783	-0.06733	-0.17424	0.086135
K95785537	PP-2	src inhibitor	IM	-0.1651	-0.0904	0.092261	0.046761	-0.12532
K96042922	etanidazole	bacterial cell wall synthesis inhibitor	MSL	-0.03599	-0.10539	-0.02357	0.032236	-0.03764
K96188950	caffeic-acid-phenethyl-ester	HIV integrase inhibitor	MSL	0.099954	0.046287	-0.14119	-0.04266	0.053387
K96194081	cepharanthine	NFkB pathway inhibitor	IM	-0.09835	-0.00833	0.098167	0.073795	-0.0749
K96259238	Y-320	interleukin inhibitor	IM	-0.17254	-0.1486	0.060313	0.193536	-0.10112
K96344439	tofogliflozin	sodium/glucose cotransporter inhibitor	IM	-0.10738	-0.13502	0.14142	0.052584	-0.0926
K96424892	chloramphenicol-palmitate	protein synthesis inhibitor	M	0.06547	0.06128	-0.09487	-0.11626	0.035937
K96874295	gonadorelin	gonadotropin releasing factor hormone receptor agonist	MSL	-0.05189	-0.10614	-0.12242	-0.01145	-0.06774
K97025174	capadenoson	adenosine receptor agonist	IM	-0.1234	-0.00185	-0.06004	0.032141	-0.02665
K97056771	GNF-2	Bcr-Abl kinase inhibitor	IM	-0.02935	-0.03304	-0.05938	-0.07177	-0.02831
K97072811	TG-003	CLK inhibitor	MSL	-0.04255	-0.10494	-0.10317	0.033961	-0.05387
K97233161	ABT-491	platelet activating factor receptor antagonist	IM	-0.10653	-0.08486	0.009812	0.046206	-0.12071

K97521363	clorsulon	glycolysis inhibitor	IM	-0.11992	-0.02813	0.105406	0.000191	-0.01243
K97564742	mepyramine	histamine receptor antagonist	IM	-0.07718	-0.15499	-0.03152	0.077879	-0.11565
K97799481	oxtriphylline	adenosine receptor antagonist	MSL	0.020445	0.039012	-0.03878	-0.08066	0.075905
K97939847	cridanimod	progesterone receptor agonist	MSL	-0.01816	-0.20219	-0.01789	0.076081	-0.17
K98251413	IOX2	hypoxia inducible factor inhibitor	IM	-0.0409	-0.04037	0.01906	0.090664	-0.06501
K98357249	IRL-2500	endothelin receptor antagonist	IM	-0.06473	-0.01191	-0.12142	0.007861	0.02691
K98572433	AZD8931	EGFR inhibitor	IM	-0.08735	-0.09307	0.403442	0.220841	0.04159
K98769987	flumazenil	benzodiazepine receptor antagonist	MSL	-0.01893	0.075314	-0.13407	-0.11148	-0.00489
K99174507	cardiogenol-c	cardiomyogenesis inducer	MSL	0.01043	-0.05174	-0.00925	-0.01984	-0.07629
K99308954	sodium-monofluorophosphate		MSL	-0.02506	0.126866	-0.08529	-0.13473	0.045039
K99447003	enalaprilat	angiotensin converting enzyme inhibitor	MSL	0.060401	0.034044	-0.1038	-0.06381	-0.03184
K99604664	tanaproget	progesterone receptor agonist	M	0.134784	0.169943	-0.04088	-0.15802	0.149326
K99621550	tubocurarine	acetylcholine receptor antagonist	MSL	-0.01099	-0.01544	-0.01951	0.057187	-0.07528
K99946902	hexylresorcinol	local anesthetic	IM	-0.13985	-0.04512	0.005622	-0.02627	-0.03629
K99964838	bosutinib	Abl kinase inhibitor; Bcr-Abl kinase inhibitor; src inhibitor	IM	-0.11177	-0.13282	0.182795	0.161122	0.000707
M63173034	clonixin-lysinate	cyclooxygenase inhibitor	MSL	-0.00484	-0.06378	-0.03679	0.004709	-0.01494

[0316] Among other things, our analyses provided valuable insights including, for example, that compounds annotated with a mechanism of action as EGFR inhibitors were significantly associated with the IM class, compounds with a mechanism of action as RAF inhibitors were significantly associated the M class, and compounds with a mechanism of action as rho associated kinase inhibitors were associated with the MSL class (Table 23B)

[0317] Table 23B: Mechanism of action and associated subtype for selected compounds with significant subtype association.

Mechanisms of Action	IM	MSL	M
adrenergic receptor agonist	9	2	0
cyclooxygenase inhibitor	5	5	1
EGFR inhibitor	21	0	0
phosphodiesterase inhibitor	5	5	2
RAF inhibitor	0	0	7
rho associated kinase inhibitor	0	6	1

[0318] The compound list was further assessed to limit associated genes to those that were present in a list of genes derived to allow for maximum diversity between clusters defined by the 101 gene signature. This list of genes consisted of a union of 937 genes derived from an analysis of lung squamous, melanoma and sarcoma tumor gene expression data sets, 936 genes from an analysis of lung squamous, lung adeno, and breast tumors, 1525 genes from a union of genes sets determined to give maximum diversity, employing the top five sets that use five unique tumor types, and 2072 genes from a union of the top three gene sets that use nine unique tumor types, resulting in 2595 unique genes. When limited to the genes also present in the cell line expression data set, this resulted in a set of 2198 genes. To remove genes with very low expression and very low variability, genes were further limited to those that had a standard deviation greater than 0.3 across the training cell lines, resulting in a final list of 1954 genes.

[0319] In addition to gene expression data, gene dependency data was analyzed. These cancer cell line genetic dependencies were estimated using the DEMETER2 model applied to three large-scale RNAi screening datasets: the Broad Institute Project Achilles, Novartis Project DRIVE, and the Marcotte et al. breast cell line dataset (Marcotte, R. et al. Functional genomic landscape of human breast cancer drivers, vulnerabilities, and

resistance. Cell 164, 293–309 (2016)), covering a total of 17309 genes and 712 unique cancer cell lines (James M. McFarland, Zandra V. Ho, Guillaume Kugener, Joshua M. Dempster, Phillip G. Montgomery, Jordan G. Bryan, John M. Krill-Burger, Thomas M. Green, Francisca Vazquez, Jesse S. Boehm, Todd R. Golub, William C. Hahn, David E. Root, Aviad Tsherniak. (2018). Improved estimation of cancer dependencies from large-scale RNAi screens using model-based normalization and data integration. Nature Communications 9, Genetic dependency was determined by examining effects of single-gene knockdowns on cell viability, which may, *e.g.*, provide information about genetic pathways that differ between the biology of diverse cell types. Gene dependence data was downloaded from the Broad Institute (https://depmap.org/portal/download/).

[0320] This list of genes (based upon gene expression and gene dependency) was analyzed by Pearson correlation with the compound sensitivity data across the training cell lines. Correlation values, p values, q values and local false discovery rates were calculated. This analysis was repeated using the same set of compounds and genes on the test set of cell lines. A list of genes was prepared for genes associated with compounds wherein (i) the q value of the correlation was less than 0.05 in both training and test sets, (ii) the correlation was negative in both training and test sets (indicating that positive gene expression would indicate increased sensitivity of the cells to the compound), and (iii) the compound had a significant negative correlation with one of the subtypes in the training set and the direction of this correlation was also found in the test set of samples, resulting in a list of 1136 gene:compound correlate pairs (Table 24A). When gene dependency was also examined, the criteria were that p values for correlations with compound sensitivity of the gene expression and gene dependency be less than 0.05 for train and test sets, the correlation was negative in both training and test sets (indicating that positive gene expression would indicate increased sensitivity of cells to the compound) and that the compound had a significant negative correlation with one of the TNBCTypes in the training set and the direction of this correlation was also found in the test set of samples resulted in a list of 60 gene:compound correlate pairs (Table 24B). Analysis of these two lists of correlate pairs provided 80 unique compounds (Table 25) and 413 unique genes (Table 26).

[0321] Table 24A: Gene:compound correlate pairs.

BROAD compound ID	Compound Name	Mechanism of Action (MoA)	Associated Gene	Associated Gene Family	compound gene train corr	compound gene train pvalue	compound gene train qvalue	compound gene test corr	TNB CType train	DTIO Corr train	TNB CType test	DTIO Corr test
A19777893	menadione-bisulfite	vitamin K	CHL1	atp-dependent dna helicase ddx11-related	-0.16405	0.002077	0.040711	-0.24587	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	COL19A1	collagen alpha-1	-0.20712	9.49E-05	0.005666	-0.2615	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	DSTYK	dual serine/threonine and tyrosine protein kinase	-0.19424	0.000256	0.010993	-0.28535	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.1722	0.001219	0.029507	-0.25535	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	FCRLA	fc receptor-like a	-0.24011	5.56E-06	0.000784	-0.26475	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	GHR	growth hormone receptor	-0.17005	0.001407	0.032213	-0.29744	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	LUM	lumican	-0.19584	0.000227	0.010178	-0.32589	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	LZTS1		-0.19066	0.000334	0.013076	-0.31334	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	NCKAP5L	nck-associated protein 5-like	-0.16478	0.001982	0.039571	-0.3161	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	P2RX7	p2x purinoceptor 7	-0.20541	0.000109	0.006199	-0.25845	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	PLEKHO1	pleckstrin homology domain-containing family o member 1	-0.16006	0.002672	0.047229	-0.25114	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	PLEKHO2	pleckstrin homology domain-containing family o member 2	-0.21275	6.02E-05	0.004166	-0.30027	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	PLP1	myelin proteolipid protein	-0.23319	1.04E-05	0.001237	-0.24224	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	PLPP7	inactive phospholipid phosphatase 7	-0.18307	0.000578	0.018506	-0.28435	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	QKI	protein quaking	-0.21643	4.45E-05	0.003384	-0.27363	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	SYNM	asparagine--trna ligase; mitochondrial-related	-0.17425	0.001063	0.027159	-0.25909	M	0 003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	TAMALIN	protein tamalin	-0.16412	0.002068	0.040597	-0.25395	M	0 003549	M	0.136223

A19777893	menadione-bisulfite	vitamin K	WWTR1	ww domain-containing transcription regulator protein 1	-0.17938	0.000748	0.021763	-0.25083	M	0.003549	M	0.136223
A19777893	menadione-bisulfite	vitamin K	ZCCHC24		-0.17083	0.001336	0.031201	-0.31612	M	0.003549	M	0.136223
A27883417	alexidine	phosphatidylglycerophosphatase inhibitor	DLX5	homeobox protein dlx-5	-0.1652	0.001736	0.03657	-0.30277	M	0.209638	M	0.100148
A56085258	LGX818	RAF inhibitor	A2M	alpha-2-macroglobulin	-0.16839	0.001185	0.028993	-0.25529	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ADAM23	disintegrin and metalloproteinase domain-containing protein 23	-0.24066	3.01E-06	0.000507	-0.28256	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	AMOTL1	angiomotin-like protein 1	-0.16334	0.001667	0.035676	-0.24815	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	APOD	apolipoprotein d	-0.2193	2.19E-05	0.002075	-0.31606	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.29218	1.12E-08	8.41E-06	-0.45115	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.38448	2.07E-14	6.2E-10	-0.50814	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	C3orf70	upf0524 protein c3orf70	-0.20964	5.06E-05	0.0037	-0.32503	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CAMK4	calcium/calmodulin-dependent protein kinase type iv	-0.16369	0.001629	0.035163	-0.24634	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CD96	t-cell surface protein tactile	-0.33386	4.96E-11	1.41E-07	-0.38369	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CDH19	cadherin-19	-0.33522	4.09E-11	1.25E-07	-0.43896	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CHL1	atp-dependent dna helicase ddx11-related	-0.29742	5.95E-09	5.24E-06	-0.31373	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CHST11	carbohydrate sulfotransferase 11	-0.21346	3.65E-05	0.002957	-0.30656	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CIITA	mhc class ii transactivator	-0.19451	0.000174	0.008515	-0.30937	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CMTM5	cklf-like marvel transmembrane domain-containing protein 5	-0.17744	0.000627	0.019495	-0.36347	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	COL19A1	collagen alpha-1	-0.33232	6.15E-11	1.67E-07	-0.4652	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	COL9A3	collagen alpha-3	-0.20705	6.29E-05	0.004297	-0.36967	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.20868	5.48E-05	0.003907	-0.32376	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.26194	3.45E-07	0.000106	-0.34344	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	CUBN	cubilin	-0.18418	0.000383	0.014241	-0.26741	M	0.095349	M	0.14417

A56085258	LGX818	RAF inhibitor	CYGB	cytoglobin	-0.29983	4.42E-09	4.2E-06	-0.28783	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.29215	1.13E-08	8.42E-06	-0.41447	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	EDNRB	endothelin receptor type b	-0.37653	7.69E-14	1.39E-09	-0.42433	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FAM180B	protein fam180b	-0.32502	1.68E-10	3.65E-07	-0.35665	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.2842	2.89E-08	1.68E-05	-0.37356	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.26403	2.76E-07	9E-05	-0.369	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FCMR	fas apoptotic inhibitory molecule 3	-0.21888	2.27E-05	0.002132	-0.33414	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FCRLA	fc receptor-like a	-0.39159	6.18E-15	2.14E-10	-0.49471	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.2932	9.93E-09	7.7E-06	-0.26766	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GAS7	growth arrest-specific protein 7	-0.28115	4.11E-08	2.19E-05	-0.46893	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GHR	growth hormone receptor	-0.1955	0.000161	0.008071	-0.23923	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GNG2	guanine nucleotide-binding protein g	-0.25005	1.19E-06	0.000259	-0.25046	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GPR55	g-protein coupled receptor 55	-0.20031	0.000109	0.006227	-0.30141	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GPSM3	g-protein-signaling modulator 3	-0.33901	2.39E-11	8.4E-08	-0.2584	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	GYPC	glycophorin-c	-0.28769	1.92E-08	1.25E-05	-0.29639	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	HPS5	hermansky-pudlak syndrome 5 protein	-0.26856	1.69E-07	6.23E-05	-0.28264	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.31955	3.51E-10	6.2E-07	-0.30361	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	IL16	pro-interleukin-16	-0.3302	8.25E-11	2.11E-07	-0.44457	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	IL24		-0.24515	1.94E-06	0.000369	-0.27469	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	IRF4	interferon regulatory factor 4	-0.37471	1.03E-13	1.66E-09	-0.43362	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ITGB3	integrin beta-3	-0.20906	5.31E-05	0.003823	-0.3046	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ITIH5	inter-alpha-trypsin inhibitor heavy chain h5	-0.19754	0.000137	0.007246	-0.29554	M	0.095349	M	0.14417

A56085258	LGX818	RAF inhibitor	KCNAB1	voltage-gated potassium channel subunit beta-1	-0.18156	0.000465	0.016145	-0.31645	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	KCNJ10	atp-sensitive inward rectifier potassium channel 10	-0.20827	5.67E-05	0.004002	-0.41309	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	KDR	vascular endothelial growth factor receptor 2	-0.21275	3.88E-05	0.003081	-0.23905	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	KIRREL1	kin of irre-like protein 1	-0.16428	0.001566	0.034351	-0.26274	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	LPXN	leupaxin	-0.2962	6.91E-09	5.87E-06	-0.30671	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	LSAMP	limbic system-associated membrane protein	-0.24444	2.08E-06	0.000388	-0.25145	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	LYL1	protein lyl-1	-0.16805	0.001213	0.029408	-0.25896	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	LZTS1		-0.25392	7.99E-07	0.000194	-0.27449	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	MCC	colorectal mutant cancer protein	-0.21255	3.95E-05	0.003116	-0.26368	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	MCOLN2	mucolipin-2	-0.2334	6.04E-06	0.000833	-0.38009	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	MIA	melanoma-derived growth regulatory protein	-0.30601	2.04E-09	2.33E-06	-0.47935	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	MMP16	matrix metalloproteinase-16	-0.20948	5.13E-05	0.003736	-0.25534	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	NFATC2	nuclear factor of activated t-cells; cytoplasmic 2	-0.26567	2.31E-07	7.87E-05	-0.3784	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.21368	3.58E-05	0.00292	-0.37252	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	NLGN1	neuroligin-1	-0.2824	3.56E-08	1.94E-05	-0.25938	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	NRP2	protein kinase c-binding protein nell2	-0.21548	3.06E-05	0.002622	-0.35039	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.29662	6.56E-09	5.64E-06	-0.32609	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	P2RX7	p2x purinoceptor 7	-0.2082	5.71E-05	0.00402	-0.26138	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PHYHIP	phytanoyl-coa hydroxylase-interacting protein	-0.19014	0.000244	0.010656	-0.29104	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PIK3CD	phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	-0.21879	2.29E-05	0.002143	-0.27445	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PKNOX2	homeobox protein pknox2	-0.23598	4.73E-06	0.000699	-0.34598	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PLEKHO2	pleckstrin homology domain-containing family o member 2	-0.21473	3.27E-05	0.002741	-0.24206	M	0.095349	M	0.14417

A56085258	LGX818	RAF inhibitor	PLP1	myelin proteolipid protein	-0.37272	1.43E-13	2.07E-09	-0.47469	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PLXNB3	plexin-b3	-0.18322	0.000411	0.014908	-0.27828	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PMP2	myelin p2 protein	-0.33787	2.81E-11	9.55E-08	-0.40268	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.3693	2.47E-13	3.07E-09	-0.45214	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	PTPRZ1	receptor-type tyrosine-protein phosphatase zeta	-0.27017	1.41E-07	5.47E-05	-0.36042	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.32001	3.3E-10	5.88E-07	-0.32171	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	RGS1	regulator of g-protein signaling 1	-0.20343	8.48E-05	0.005251	-0.31782	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.33576	3.79E-11	1.2E-07	-0.33613	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SGCD	delta-sarcoglycan	-0.31183	9.67E-10	1.35E-06	-0.38792	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SHC4	shc-transforming protein 4	-0.29815	5.44E-09	4.9E-06	-0.3808	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SHROOM4	protein shroom4	-0.25342	8.42E-07	0.000202	-0.28424	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SLC35F1	solute carrier family 35 member f1	-0.2225	1.65E-05	0.001709	-0.39285	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SNX10	sorting nexin-10	-0.24148	2.78E-06	0.000477	-0.24704	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.25559	6.73E-07	0.000172	-0.34323	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SOX5	transcription factor sox-5	-0.21892	2.27E-05	0.002127	-0.28721	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	SRPX	sushi repeat-containing protein srpx	-0.31846	4.06E-10	6.86E-07	-0.33494	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ST3GAL5	lactosylceramide alpha-2,3-sialyltransferase	-0.16324	0.001679	0.035844	-0.29017	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ST6GALNAC3	alpha-n-acetylgalactosaminide alpha-2,6-sialyltransferase 3	-0.25362	8.24E-07	0.000199	-0.27653	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2,8-sialyltransferase	-0.29567	7.36E-09	6.16E-06	-0.36897	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	STK10	serine/threonine-protein kinase 10	-0.23813	3.85E-06	0.000605	-0.31685	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	STK32B	serine/threonine-protein kinase 32b	-0.19392	0.000182	0.008775	-0.26921	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	TAMALIN	protein tamalin	-0.23509	5.15E-06	0.000741	-0.33024	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	TIMP3	metalloproteinase inhibitor 3	-0.18821	0.000283	0.011719	-0.24226	M	0.095349	M	0.14417

A56085258	LGX818	RAF inhibitor	TMEM229B	transmembrane protein 229b	-0.24112	2.88E-06	0.00049	-0.32045	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	TNFRSF14	tumor necrosis factor receptor superfamily member 14	-0.25238	9.36E-07	0.000218	-0.28053	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.36439	5.36E-13	5.3E-09	-0.39013	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	WARS1	tryptophan--trna ligase, cytoplasmic	-0.16727	0.001279	0.030381	-0.27796	M	0.095349	M	0.14417
A56085258	LGX818	RAF inhibitor	WWTR1	ww domain-containing transcription regulator protein 1	-0.19172	0.000216	0.00985	-0.30705	M	0.095349	M	0.14417
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ANKRD44	serine/threonine-protein phosphatase 6 regulatory ankyrin repeat subunit b	-0.18164	0.000639	0.019713	-0.30286	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	APOD	apolipoprotein d	-0.25176	1.84E-06	0.000356	-0.29484	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.18683	0.000442	0.015634	-0.30528	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	BCL2A1	bcl-2-related protein a1	-0.32445	5.06E-10	8.19E-07	-0.34688	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	C3orf70	upf0524 protein c3orf70	-0.19028	0.000344	0.013311	-0.33214	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	CD96	t-cell surface protein tactile	-0.22373	2.4E-05	0.002208	-0.24228	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	CDH19	cadherin-19	-0.31627	1.43E-09	1.82E-06	-0.29508	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	COL19A1	collagen alpha-1	-0.34976	1.65E-11	6.55E-08	-0.35543	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	COL9A3	collagen alpha-3	-0.24685	2.95E-06	0.000499	-0.24857	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.26527	4.77E-07	0.000134	-0.29153	M	0.119134	M	0.165805

A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.22865	1.56E-05	0.001649	-0.34779	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.23336	1.03E-05	0.001224	-0.31521	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	DSTYK	dual serine/threonine and tyrosine protein kinase	-0.17162	0.001268	0.030229	-0.24859	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	EDNRB	endothelin receptor type b	-0.30706	4.45E-09	4.22E-06	-0.32819	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FAM180B	protein fam180b	-0.28668	4.78E-08	2.46E-05	-0.34598	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.30101	9.19E-09	7.28E-06	-0.31337	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.35978	3.91E-12	2.15E-08	-0.29889	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FCMR	fas apoptotic inhibitory molecule 3	-0.18407	0.000538	0.017725	-0.24024	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FCRLA	fc receptor-like a	-0.32029	8.63E-10	1.25E-06	-0.3519	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.26882	3.3E-07	0.000103	-0.2531	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	GAS7	growth arrest-specific protein 7	-0.31592	1.5E-09	1.87E-06	-0.39688	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	GNG2	guanine nucleotide-binding protein g	-0.24382	3.93E-06	0.000613	-0.25932	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	GPR55	g-protein coupled receptor 55	-0.31557	1.56E-09	1.92E-06	-0.25541	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.19281	0.000285	0.011792	-0.28119	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	IL16	pro-interleukin-16	-0.35047	1.5E-11	6.07E-08	-0.39888	M	0.119134	M	0.165805

A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	IRF4	interferon regulatory factor 4	-0.30026	1E-08	7.75E-06	-0.36836	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ITGA10	integrin alpha-10	-0.24995	2.19E-06	0.000401	-0.27543	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	LCP2	lymphocyte cytosolic protein 2	-0.22068	3.11E-05	0.002648	-0.25768	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	LPXN	leupaxin	-0.2009	0.000155	0.007868	-0.27465	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	LYL1	protein lyl-1	-0.20291	0.000132	0.007083	-0.23968	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	LZTS1		-0.2615	7E-07	0.000177	-0.26423	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	MIA	melanoma-derived growth regulatory protein	-0.28781	4.21E-08	2.23E-05	-0.31384	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	MMP16	matrix metalloproteinase-16	-0.22993	1.4E-05	0.001524	-0.25299	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	NES	nestin	-0.26536	4.72E-07	0.000133	-0.26762	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.27791	1.26E-07	5.03E-05	-0.30984	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	PKNOX2	homeobox protein pknox2	-0.30913	3.47E-09	3.48E-06	-0.28024	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	PLP1	myelin proteolipid protein	-0.34609	2.77E-11	9.44E-08	-0.40769	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	PLXNC1	plexin-c1	-0.25315	1.61E-06	0.000322	-0.25776	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	PMP2	myelin p2 protein	-0.36606	1.54E-12	1.15E-08	-0.28479	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.39041	3.44E-14	8.59E-10	-0.31291	M	0.119134	M	0.165805

A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.21826	3.82E-05	0.003048	-0.24478	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	RGS1	regulator of g-protein signaling 1	-0.2271	1.79E-05	0.001807	-0.27054	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.25427	1.44E-06	0.000297	-0.32588	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SCML4	sex comb on midleg-like protein 4	-0.31482	1.72E-09	2.04E-06	-0.29816	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SGCA	alpha-sarcoglycan	-0.19417	0.000258	0.011027	-0.25087	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SGCD	delta-sarcoglycan	-0.31226	2.36E-09	2.63E-06	-0.28906	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SHC4	shc-transforming protein 4	-0.32394	5.41E-10	8.56E-07	-0.35193	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.3851	8.09E-14	1.4E-09	-0.25216	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SOX5	transcription factor sox-5	-0.22526	2.1E-05	0.002013	-0.33593	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	SRPX	sushi repeat-containing protein srpx	-0.19752	0.0002	0.009368	-0.25374	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ST3GAL5	lactosylceramide alpha-2;3-sialyltransferase	-0.18288	0.000586	0.018659	-0.26128	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ST6GALNAC3	alpha-n-acetylgalactosaminide alpha-2;6-sialyltransferase 3	-0.19973	0.000169	0.008361	-0.3294	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2;8-sialyltransferase	-0.28571	5.33E-08	2.65E-05	-0.25987	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	STK10	serine/threonine-protein kinase 10	-0.18937	0.000368	0.013886	-0.28438	M	0.119134	M	0.165805
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	TMEM229B	transmembrane protein 229b	-0.19281	0.000285	0.011792	-0.2699	M	0.119134	M	0.165805

A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.32538	4.49E-10	7.43E-07	-0.35086	M	0.119134	M	0.165805
K01507359	rifampin	RNA polymerase inhibitor	SCARF2	scavenger receptor class f member 2	-0.2038	0.000141	0.0074	-0.24517	M	0.115452	M	0.057333
K01507359	rifampin	RNA polymerase inhibitor	SMO	smoothened homolog	-0.17829	0.000895	0.024378	-0.25815	M	0.115452	M	0.057333
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.28971	3.4E-08	1.87E-05	-0.3009	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	COL17A1	collagen alpha-1	-0.32929	2.69E-10	5.06E-07	-0.32705	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.20759	9.14E-05	0.005516	-0.28528	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.32567	4.32E-10	7.21E-07	-0.35713	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.23544	8.52E-06	0.00107	-0.29093	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	DSG3	desmoglein-3	-0.37003	8.47E-13	7.33E-09	-0.33926	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	FBLN1	fibulin-1	-0.17862	0.000789	0.022494	-0.26582	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.18603	0.000468	0.016223	-0.31842	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	ITGB4	integrin beta-4	-0.3122	2.38E-09	2.64E-06	-0.37313	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	KRT14	keratin; type i cytoskeletal 14	-0.33812	8.28E-11	2.11E-07	-0.25953	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.324	5.37E-10	8.51E-07	-0.39867	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.33778	8.68E-11	2.18E-07	-0.28994	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.3793	2.03E-13	2.6E-09	-0.36773	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	MAPK10	mitogen-activated protein kinase 10	-0.19522	0.000238	0.010489	-0.24025	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	PLAAT4	phospholipase a and acyltransferase 4	-0.22419	2.3E-05	0.002149	-0.23913	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.32275	6.3E-10	9.65E-07	-0.40649	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.30807	3.94E-09	3.85E-06	-0.36363	IM	-0.1539	IM	-0.05086

K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	S100A8	protein s100-a8	-0.24965	2.26E-06	0.000409	-0.31627	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.25355	1.55E-06	0.000314	-0.29342	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	TNFAIP8	tumor necrosis factor alpha-induced protein 8	-0.31651	1.39E-09	1.78E-06	-0.25194	IM	-0.1539	IM	-0.05086
K03765900	XL-647	EGFR inhibitor; VEGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.322	6.93E-10	1.04E-06	-0.31438	IM	-0.1539	IM	-0.05086
K04568635	octenidine	membrane integrity inhibitor	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.18264	0.000506	0.017021	-0.2787	M	0.147947	M	0.09423
K04568635	octenidine	membrane integrity inhibitor	CERS1	ceramide synthase 1	-0.17362	0.000955	0.025405	-0.23784	M	0.147947	M	0.09423
K04568635	octenidine	membrane integrity inhibitor	FAM78A	protein fam78a	-0.23004	1.07E-05	0.00126	-0.28623	M	0.147947	M	0.09423
K05804044	AZ-628	RAF inhibitor	A2M	alpha-2-macroglobulin	-0.21111	4.91E-05	0.003627	-0.27125	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	AEBP1	adipocyte enhancer-binding protein 1	-0.17089	0.001063	0.02716	-0.26693	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	APOD	apolipoprotein d	-0.22873	1.05E-05	0.001239	-0.41082	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.24031	3.53E-06	0.000571	-0.36012	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.3244	2.29E-10	4.48E-07	-0.36448	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	C3orf70	upf0524 protein c3orf70	-0.25107	1.22E-06	0.000265	-0.32375	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CDH19	cadherin-19	-0.36232	9.85E-13	8.42E-09	-0.33307	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CHL1	atp-dependent dna helicase ddx11-related	-0.23777	4.5E-06	0.000673	-0.24278	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CMTM5	cklf-like marvel transmembrane domain-containing protein 5	-0.17157	0.001014	0.026393	-0.2448	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	COL19A1	collagen alpha-1	-0.30838	1.85E-09	2.16E-06	-0.41797	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	COL9A3	collagen alpha-3	-0.32496	2.13E-10	4.22E-07	-0.39502	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.27418	1.07E-07	4.46E-05	-0.27405	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.24944	1.44E-06	0.000298	-0.29473	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	CYGB	cytoglobin	-0.27288	1.23E-07	4.96E-05	-0.34369	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.23311	6.98E-06	0.000926	-0.30063	M	0.190801	M	0.324717

K05804044	AZ-628	RAF inhibitor	EDNRB	endothelin receptor type b	-0.3548	3.08E-12	1.82E-08	-0.33929	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FAM180B	protein fam180b	-0.32371	2.52E-10	4.84E-07	-0.39105	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FCER1G	high affinity immunoglobulin epsilon receptor subunit gamma	-0.21898	2.5E-05	0.002275	-0.29011	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.25237	1.07E-06	0.000242	-0.28154	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.26349	3.39E-07	0.000105	-0.30444	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FCMR	fas apoptotic inhibitory molecule 3	-0.16428	0.001662	0.035608	-0.28415	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FCRLA	fc receptor-like a	-0.35543	2.8E-12	1.7E-08	-0.41839	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.30989	1.53E-09	1.89E-06	-0.26232	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GAS7	growth arrest-specific protein 7	-0.36714	4.66E-13	4.86E-09	-0.43906	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GHR	growth hormone receptor	-0.22392	1.62E-05	0.001687	-0.28625	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GNG2	guanine nucleotide-binding protein g	-0.25017	1.34E-06	0.000282	-0.30488	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GNG7	guanine nucleotide-binding protein g	-0.20408	8.79E-05	0.005379	-0.27393	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GPR55	g-protein coupled receptor 55	-0.22022	2.24E-05	0.002112	-0.28355	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	GSN	gelsolin	-0.24292	2.74E-06	0.000473	-0.28737	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.34893	7.35E-12	3.52E-08	-0.29022	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	IL16	pro-interleukin-16	-0.33604	4.65E-11	1.37E-07	-0.48581	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	IRF4	interferon regulatory factor 4	-0.34483	1.33E-11	5.54E-08	-0.41488	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	ITGA10	integrin alpha-10	-0.16659	0.001424	0.032446	-0.2449	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	ITGA9	integrin alpha-9	-0.27837	6.67E-08	3.12E-05	-0.24282	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	KCNAB1	voltage-gated potassium channel subunit beta-1	-0.21814	2.69E-05	0.002394	-0.24308	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	KCNJ10	atp-sensitive inward rectifier potassium channel 10	-0.22282	1.78E-05	0.001801	-0.3229	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	LZTS1		-0.22945	9.79E-06	0.001182	-0.3171	M	0.190801	M	0.324717

K05804044	AZ-628	RAF inhibitor	MCC	colorectal mutant cancer protein	-0.1989	0.000134	0.00713	-0.26763	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	MCOLN2	mucolipin-2	-0.16957	0.001163	0.028698	-0.28064	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	MIA	melanoma-derived growth regulatory protein	-0.33918	2.99E-11	1E-07	-0.38091	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	NES	nestin	-0.27824	6.77E-08	3.16E-05	-0.33874	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	NFATC2	nuclear factor of activated t-cells; cytoplasmic 2	-0.28168	4.58E-08	2.38E-05	-0.37529	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.17179	0.000999	0.026137	-0.32097	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	NPL	n-acetylneuraminate lyase	-0.20293	9.66E-05	0.005734	-0.24924	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.26266	3.7E-07	0.000111	-0.33699	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PKNOX2	homeobox protein pknox2	-0.27144	1.44E-07	5.55E-05	-0.32605	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PLP1	myelin proteolipid protein	-0.38023	5.76E-14	1.17E-09	-0.38754	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PLXNB3	plexin-b3	-0.22015	2.26E-05	0.002122	-0.26462	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PMP2	myelin p2 protein	-0.32496	2.13E-10	4.22E-07	-0.36738	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.33169	8.51E-11	2.15E-07	-0.40565	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	PTPRZ1	receptor-type tyrosine-protein phosphatase zeta	-0.21559	3.36E-05	0.002791	-0.31658	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.22573	1.37E-05	0.001505	-0.35896	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	RGS1	regulator of g-protein signaling 1	-0.28769	2.29E-08	1.42E-05	-0.29038	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.26239	3.81E-07	0.000114	-0.29784	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SCML4	sex comb on midleg-like protein 4	-0.27062	1.58E-07	5.93E-05	-0.30325	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SCRG1	scrapie-responsive protein 1	-0.22836	1.08E-05	0.001268	-0.25315	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SGCD	delta-sarcoglycan	-0.29116	1.52E-08	1.06E-05	-0.31726	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SH3BP1	bargin-related	-0.19178	0.000233	0.010329	-0.35291	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SHC4	shc-transforming protein 4	-0.31312	1.01E-09	1.4E-06	-0.3485	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.333	7.11E-11	1.86E-07	-0.31767	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	SOX5	transcription factor sox-5	-0.24005	3.62E-06	0.00058	-0.26172	M	0.190801	M	0.324717

K05804044	AZ-628	RAF inhibitor	ST3GAL5	lactosylceramide alpha-2;3-sialyltransferase	-0.17173	0.001003	0.026207	-0.27252	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2;8-sialyltransferase	-0.29964	5.49E-09	4.93E-06	-0.27099	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	STK10	serine/threonine-protein kinase 10	-0.16439	0.001649	0.035446	-0.26021	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	TAMALIN	protein tamalin	-0.23971	3.74E-06	0.000593	-0.24244	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	TIMP3	metalloproteinase inhibitor 3	-0.21966	2.35E-05	0.00218	-0.28658	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	TMEM229B	transmembrane protein 229b	-0.21657	3.08E-05	0.002632	-0.30604	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	TNFRSF14	tumor necrosis factor receptor superfamily member 14	-0.26507	2.87E-07	9.23E-05	-0.32016	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.35718	2.16E-12	1.45E-08	-0.34489	M	0.190801	M	0.324717
K05804044	AZ-628	RAF inhibitor	WFDC1	wap four-disulfide core domain protein 1	-0.21807	2.71E-05	0.002404	-0.30701	M	0.190801	M	0.324717
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	ADAM8	disintegrin and metalloproteinase domain-containing protein 8	-0.16357	0.001742	0.036642	-0.2475	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.18003	0.000558	0.018103	-0.39479	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.24397	2.48E-06	0.000439	-0.30311	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	COL17A1	collagen alpha-1	-0.31878	4.84E-10	7.91E-07	-0.38241	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	CXCL16	c-x-c motif chemokine 16	-0.25418	8.94E-07	0.000211	-0.30013	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	CYP4B1	cytochrome p450 4b1	-0.18372	0.000426	0.015278	-0.36885	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.32404	2.41E-10	4.68E-07	-0.42856	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	DENND1C	denn domain-containing protein 1c	-0.30086	4.73E-09	4.4E-06	-0.37138	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	DENND2D	denn domain-containing protein 2d	-0.21421	3.78E-05	0.003028	-0.28809	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	DSG3	desmoglein-3	-0.37826	7.94E-14	1.4E-09	-0.27403	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.29471	9.98E-09	7.72E-06	-0.40975	IM	-0.07697	IM	-0.02871

K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.18696	0.000335	0.013102	-0.37526	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	ITGB4	integrin beta-4	-0.36154	1.11E-12	8.77E-09	-0.45377	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.36363	8.05E-13	7.04E-09	-0.36269	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.34243	1.88E-11	7.13E-08	-0.32754	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.3821	4.24E-14	9.54E-10	-0.33086	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	LGALS9	galectin-9	-0.19215	0.000226	0.010143	-0.25463	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.2942	1.06E-08	8.07E-06	-0.32056	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	MFNG	beta-1,3-n-acetylglucosaminyltransferase manic fringe	-0.25803	6.01E-07	0.000159	-0.26797	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	PTAFR	platelet-activating factor receptor	-0.32355	2.57E-10	4.89E-07	-0.45066	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.3556	2.73E-12	1.68E-08	-0.42466	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	S100A8	protein s100-a8	-0.25994	4.93E-07	0.000137	-0.26807	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	SH3BP1	bargin-related	-0.26612	2.56E-07	8.52E-05	-0.29862	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	TEAD3	transcriptional enhancer factor tef-5	-0.26609	2.57E-07	8.54E-05	-0.25365	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	TNFAIP8	tumor necrosis factor alpha-induced protein 8	-0.19633	0.000164	0.008171	-0.23935	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.29818	6.56E-09	5.64E-06	-0.33751	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	UNC13D	protein unc-13 homolog d	-0.17233	0.000963	0.025528	-0.3177	IM	-0.07697	IM	-0.02871
K07106112	BMS-599626	EGFR inhibitor; protein tyrosine kinase inhibitor	VIPR1	vasoactive intestinal polypeptide receptor 1	-0.19563	0.000173	0.008489	-0.31868	IM	-0.07697	IM	-0.02871
K09416995	lovastatin	HMGCR inhibitor	ANGPTL7	angiopoietin-related protein 7	-0.19501	0.000185	0.008874	-0.23758	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	ARMCX1	armadillo repeat-containing x-linked protein 1	-0.16082	0.002116	0.041176	-0.26346	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.15944	0.002313	0.043375	-0.31573	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	CYBRD1	cytochrome b reductase 1	-0.19789	0.000148	0.007636	-0.26214	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	EPHA3	ephrin type-a receptor 3	-0.21134	4.94E-05	0.00364	-0.257	M	0.051166	M	0.05706

K09416995	lovastatin	HMGCR inhibitor	EVC	ellis-van creveld syndrome protein	-0.17333	0.000912	0.024666	-0.25736	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	FGL2	fibroleukin	-0.1825	0.000475	0.016369	-0.26056	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	MMP16	matrix metalloproteinase-16	-0.19006	0.000271	0.01139	-0.26083	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	PDE1C	calcium/calmodulin-dependent 3',5'-cyclic nucleotide phosphodiesterase 1c	-0.22554	1.44E-05	0.001555	-0.29327	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	PTN	pleiotrophin	-0.20096	0.000116	0.006479	-0.23928	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	RASSF8	ras association domain-containing protein 8	-0.17504	0.00081	0.022883	-0.25575	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	REEP2	receptor expression-enhancing protein 2	-0.16027	0.002192	0.04206	-0.26037	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.24636	2.02E-06	0.00038	-0.31485	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	SCRG1	scrapie-responsive protein 1	-0.24725	1.85E-06	0.000358	-0.24415	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	SPARC	sparc	-0.19645	0.000165	0.008241	-0.25228	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	SRPX	sushi repeat-containing protein srpx	-0.25233	1.12E-06	0.000249	-0.23894	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.23875	4.23E-06	0.000644	-0.26759	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	TIMP2	metalloproteinase inhibitor 2	-0.18333	0.000447	0.015746	-0.24673	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	TMEM255A	transmembrane protein 255a	-0.15727	0.002657	0.047066	-0.29772	M	0.051166	M	0.05706
K09416995	lovastatin	HMGCR inhibitor	VIM	vimentin	-0.20599	7.7E-05	0.004925	-0.25451	M	0.051166	M	0.05706
K13060017	UNC0631	histone lysine methyltransferase inhibitor	CHL1	atp-dependent dna helicase ddx11-related	-0.19048	0.000326	0.012863	-0.24128	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	COL19A1	collagen alpha-1	-0.25277	1.56E-06	0.000315	-0.2431	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.15961	0.002673	0.047237	-0.29838	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	CST7	cystatin-f	-0.17664	0.000873	0.023992	-0.33144	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.16242	0.002238	0.042566	-0.3327	M	0.105455	M	0.163017

K13060017	UNC0631	histone lysine methyltransferase inhibitor	EDNRB	endothelin receptor type b	-0.20035	0.000154	0.007863	-0.27429	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	GNG2	guanine nucleotide-binding protein g	-0.22329	2.36E-05	0.002182	-0.31662	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	HMCN1	hemicentin-1	-0.16061	0.00251	0.045491	-0.33456	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	IL16	pro-interleukin-16	-0.21748	3.87E-05	0.003076	-0.31353	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	LSAMP	limbic system-associated membrane protein	-0.16546	0.00184	0.037877	-0.26388	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	LZTS1		-0.16602	0.001775	0.037078	-0.2903	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.17863	0.000761	0.021993	-0.31638	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	P2RX7	p2x purinoceptor 7	-0.22645	1.79E-05	0.001808	-0.30062	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	PLEKHO2	pleckstrin homology domain-containing family o member 2	-0.17007	0.001361	0.03155	-0.30906	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	PLP1	myelin proteolipid protein	-0.21155	6.33E-05	0.004314	-0.26933	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	PLXNB3	plexin-b3	-0.20018	0.000156	0.007925	-0.24736	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	RCN2	reticulocalbin-2	-0.17331	0.001095	0.027688	-0.29837	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	SGCD	delta-sarcoglycan	-0.15902	0.002772	0.048275	-0.291	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	SRPX	sushi repeat-containing protein srpx	-0.16955	0.001409	0.032234	-0.33386	M	0.105455	M	0.163017
K13060017	UNC0631	histone lysine methyltransferase inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2;8-sialyltransferase	-0.22286	2.45E-05	0.002242	-0.24416	M	0.105455	M	0.163017

K13060017	UNC0631	histone lysine methyltransferase inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.25497	1.25E-06	0.00027	-0.26572	M	0.105455	M	0.163017
K13183738	pentamidine	anti-pneumocystis agent	ACACB	acetyl-coa carboxylase 2	-0.15713	0.002646	0.046937	-0.26193	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.19946	0.000128	0.006925	-0.27135	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	DVL2	segment polarity protein dishevelled homolog dvl-2	-0.19711	0.000154	0.007843	-0.30089	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	JAM3	junctional adhesion molecule c	-0.15815	0.002478	0.045153	-0.24591	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	MPP2	forkhead box protein m1	-0.16459	0.001628	0.035152	-0.28632	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	PDZD4	pdz domain-containing protein 4	-0.20438	8.58E-05	0.005296	-0.26962	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.15586	0.002867	0.04925	-0.3033	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	SMO	smoothened homolog	-0.27546	9.24E-08	3.98E-05	-0.2583	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	TAMALIN	protein tamalin	-0.17156	0.001015	0.026407	-0.25341	M	0.215745	M	0.139961
K13183738	pentamidine	anti-pneumocystis agent	TUB	tubby protein homolog	-0.27417	1.07E-07	4.46E-05	-0.26021	M	0.215745	M	0.139961
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ADAMTS1	a disintegrin and metalloproteinase with thrombospondin motifs 1	-0.19165	0.000299	0.012145	-0.31976	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ADAMTS9	a disintegrin and metalloproteinase with thrombospondin motifs 9	-0.31119	2.43E-09	2.69E-06	-0.31362	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ANKRD44	serine/threonine-protein phosphatase 6 regulatory ankyrin repeat subunit b	-0.20261	0.000129	0.006982	-0.28974	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ANTXR1	anthrax toxin receptor 1	-0.2193	3.32E-05	0.002769	-0.27465	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ARHGAP31	rho gtpase-activating protein 31	-0.21331	5.48E-05	0.003904	-0.28188	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	BCL2A1	bcl-2-related protein a1	-0.19582	0.000218	0.009928	-0.31153	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	C3AR1	c3a anaphylatoxin chemotactic receptor	-0.18512	0.000481	0.0165	-0.31536	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CALD1	caldesmon	-0.2835	6.25E-08	2.98E-05	-0.32385	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CCN2	ccn family member 2	-0.18819	0.000385	0.014297	-0.25238	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CD96	t-cell surface protein tactile	-0.29422	1.85E-08	1.22E-05	-0.37879	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CDH19	cadherin-19	-0.28672	4.36E-08	2.29E-05	-0.31266	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CERKL	ceramide kinase-like protein	-0.20404	0.000116	0.006479	-0.28662	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	COL19A1	collagen alpha-1	-0.26962	2.81E-07	9.1E-05	-0.29878	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	COL4A2	collagen alpha-2	-0.18956	0.000349	0.013431	-0.31187	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CPQ	carboxypeptidase q	-0.28128	7.99E-08	3.58E-05	-0.29139	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.17729	0.000835	0.023313	-0.29778	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.22705	1.7E-05	0.001747	-0.24734	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	DAAM2	dishevled-associated activator of morphogenesis 2	-0.18851	0.000376	0.0141	-0.35354	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	DLC1	rho gtpase-activating protein 7	-0.29197	2.4E-08	1.47E-05	-0.24823	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	DRAM1	dna damage-regulated autophagy modulator protein 1	-0.17328	0.001098	0.027735	-0.27887	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	EDNRB	endothelin receptor type b	-0.25011	2.02E-06	0.00038	-0.24971	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	EPHA3	ephrin type-a receptor 3	-0.17155	0.001233	0.029726	-0.2452	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.28126	8.01E-08	3.59E-05	-0.2796	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FCRLA	fc receptor-like a	-0.2598	7.73E-07	0.00019	-0.32843	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FERMT2	fermitin family homolog 2	-0.24825	2.42E-06	0.00043	-0.26591	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FKBP7	peptidyl-prolyl cis-trans isomerase fkbp7	-0.21984	3.17E-05	0.002684	-0.24966	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.17472	0.000995	0.026069	-0.31053	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	FN1	fibronectin	-0.27474	1.63E-07	6.07E-05	-0.26405	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	GAS7	growth arrest-specific protein 7	-0.25575	1.16E-06	0.000256	-0.28382	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	GDNF	glial cell line-derived neurotrophic factor	-0.19768	0.00019	0.009029	-0.28533	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	GYPC	glycophorin-c	-0.23894	5.82E-06	0.00081	-0.27453	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	HEG1	protein heg homolog 1	-0.17654	0.000879	0.024099	-0.25485	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	HPS5	hermansky-pudlak syndrome 5 protein	-0.2768	1.3E-07	5.17E-05	-0.35554	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	IGFBP7	insulin-like growth factor-binding protein 7	-0.23741	6.7E-06	0.000898	-0.25232	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ITGA4	integrin alpha-4	-0.19276	0.000275	0.011515	-0.27254	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	ITGB3	integrin beta-3	-0.41144	8.19E-16	4.61E-11	-0.42256	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	KIRREL1	kin of irre-like protein 1	-0.29106	2.66E-08	1.59E-05	-0.41603	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	KLHL29	kelch-like protein 29	-0.16538	0.001851	0.038	-0.26831	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	KRBA1	protein krba1	-0.22422	2.18E-05	0.002066	-0.2633	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	LAMA4	laminin subunit alpha-4	-0.19623	0.000212	0.009724	-0.2547	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	LARP6	la-related protein 6	-0.18912	0.00036	0.013714	-0.25689	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	LZTS1		-0.26537	4.37E-07	0.000125	-0.30303	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MCAM	cell surface glycoprotein muc18	-0.22147	2.76E-05	0.002434	-0.3214	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MFGE8	lactadherin	-0.18261	0.000576	0.018465	-0.31014	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MIA	melanoma-derived growth regulatory protein	-0.20592	9.96E-05	0.005855	-0.29543	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MMP16	matrix metalloproteinase-16	-0.23044	1.26E-05	0.001414	-0.27895	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MOXD1	dbh-like monooxygenase protein 1	-0.22178	2.69E-05	0.00239	-0.31384	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MPDZ	multiple pdz domain protein	-0.20909	7.73E-05	0.004938	-0.2474	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MYH10	myosin-10	-0.28316	6.49E-08	3.06E-05	-0.30504	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	MYLK	myosin light chain kinase; smooth muscle	-0.21442	4.99E-05	0.003669	-0.27379	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	NLGN1	neuroligin-1	-0.24202	4.37E-06	0.000659	-0.29507	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.18248	0.000581	0.018573	-0.2668	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	OBSL1	obscurin-like protein 1	-0.1858	0.000458	0.016001	-0.25411	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PDE1C	calcium/calmodulin-dependent 3',5'-cyclic nucleotide phosphodiesterase 1c	-0.20544	0.000104	0.006004	-0.30418	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PDE7B	camp-specific 3',5'-cyclic phosphodiesterase 7b	-0.20025	0.000155	0.007898	-0.24596	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PIK3CD	phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	-0.16595	0.001784	0.037181	-0.33482	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PKNOX2	homeobox protein pknox2	-0.18428	0.000511	0.017132	-0.25483	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PLP1	myelin proteolipid protein	-0.28877	3.46E-08	1.9E-05	-0.35348	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PRTG	protogenin	-0.33409	1.26E-10	2.89E-07	-0.25364	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PTPRM	receptor-type tyrosine-protein phosphatase mu	-0.30591	4.63E-09	4.35E-06	-0.29048	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	QKI	protein quaking	-0.21829	3.61E-05	0.002939	-0.24849	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	RASSF4	ras and rab interactor 2	-0.20577	0.000101	0.005902	-0.26113	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	RASSF8	ras association domain-containing protein 8	-0.25558	1.18E-06	0.000258	-0.33255	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.26385	5.12E-07	0.000141	-0.29192	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	RUSC2	iporin	-0.20522	0.000105	0.006078	-0.25492	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SCARA5	scavenger receptor class a member 5	-0.17385	0.001056	0.027058	-0.27249	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SHC4	shc-transforming protein 4	-0.2357	7.84E-06	0.001008	-0.24436	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SHISA4	protein shisa-4	-0.25597	1.13E-06	0.000252	-0.32166	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SHROOM4	protein shroom4	-0.29439	1.81E-08	1.2E-05	-0.39439	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SLC35F1	solute carrier family 35 member f1	-0.17641	0.000887	0.024239	-0.32088	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SLC6A12	sodium- and chloride-dependent betaine transporter	-0.23217	1.08E-05	0.001266	-0.26619	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SNX10	sorting nexin-10	-0.27382	1.8E-07	6.54E-05	-0.27325	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.17359	0.001075	0.02736	-0.27511	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SPARC	sparc	-0.21202	6.09E-05	0.004199	-0.31662	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SPART	spartin	-0.2644	4.83E-07	0.000135	-0.35682	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SRGN		-0.21734	3.92E-05	0.0031	-0.25978	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SRPX	sushi repeat-containing protein srpx	-0.27636	1.37E-07	5.34E-05	-0.2889	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	STK32B	serine/threonine-protein kinase 32b	-0.25703	1.02E-06	0.000233	-0.35902	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.32736	3.09E-10	5.59E-07	-0.29724	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	TIMP2	metalloproteinase inhibitor 2	-0.21403	5.16E-05	0.003754	-0.26124	M	0.148517	M	0.090307
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.2301	1.3E-05	0.001444	-0.24959	M	0.148517	M	0.090307

K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	WWTR1	ww domain-containing transcription regulator protein 1	-0.29433	1.83E-08	1.21E-05	-0.39193	M	0.148517	M	0.090307
K19333160	RKI-1447	rho associated kinase inhibitor	ACTR3B	actin-related protein 3b-related	-0.16962	0.001124	0.028133	-0.2398	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	ARL10	adp-ribosylation factor-like protein 10	-0.16253	0.001812	0.03753	-0.27817	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	CHST10	carbohydrate sulfotransferase 10	-0.16296	0.00176	0.036891	-0.2705	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	CNTNAP1	contactin-associated protein 1	-0.27527	8.7E-08	3.81E-05	-0.25274	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	DACT3	dapper homolog 3	-0.30877	1.59E-09	1.94E-06	-0.27605	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	DLX2	homeobox protein dlx-2	-0.16526	0.001511	0.033626	-0.2927	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	GPR162	g-protein coupled receptor 162-related	-0.25479	7.83E-07	0.000191	-0.28022	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	GPSM1	g-protein-signaling modulator 1	-0.27133	1.35E-07	5.29E-05	-0.24569	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	HAND2	heart- and neural crest derivatives-expressed protein 2	-0.25588	7E-07	0.000177	-0.27974	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	HGF	hepatocyte growth factor	-0.163	0.001756	0.036826	-0.26698	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	JAM3	junctional adhesion molecule c	-0.24893	1.42E-06	0.000294	-0.31976	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	KBTBD6	kelch repeat and btb domain-containing protein 6	-0.16061	0.002056	0.04045	-0.24298	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	KIF5A	kinesin heavy chain isoform 5a	-0.26001	4.55E-07	0.000129	-0.2515	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	KRBA1	protein krba1	-0.19805	0.000137	0.007254	-0.24991	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	LIX1L	lix1-like protein	-0.23916	3.71E-06	0.000589	-0.23907	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	MICU3	calcium uptake protein 3; mitochondrial	-0.21213	4.3E-05	0.003303	-0.27166	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	NLGN2	neuroligin-2	-0.24685	1.75E-06	0.000342	-0.24008	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	NUDT11	diphosphoinositol polyphosphate phosphohydrolase 3-beta	-0.2279	1.07E-05	0.001258	-0.24921	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	PIANP	plir alpha-associated neural protein	-0.26366	3.09E-07	9.79E-05	-0.24854	MSL	0.046328	MSL	0.081223

K19333160	RKI-1447	rho associated kinase inhibitor	PLEKHO1	pleckstrin homology domain-containing family o member 1	-0.21951	2.27E-05	0.002127	-0.2815	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	PLPP7	inactive phospholipid phosphatase 7	-0.29234	1.21E-08	8.91E-06	-0.31957	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	RTL5	retrotransposon gag-like protein 5	-0.19173	0.000224	0.010099	-0.30955	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	SMO	smoothened homolog	-0.18192	0.000469	0.016249	-0.2961	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	STARD9	star-related lipid transfer protein 9	-0.22352	1.59E-05	0.001665	-0.30703	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	VASH1	tubulinyl-tyr carboxypeptidase 1	-0.26064	4.26E-07	0.000123	-0.25725	MSL	0.046328	MSL	0.081223
K19333160	RKI-1447	rho associated kinase inhibitor	ZEB1	zinc finger e-box-binding homeobox 1	-0.22431	1.48E-05	0.001586	-0.24296	MSL	0.046328	MSL	0.081223
K19540840	saracatinib	src inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.22658	1.14E-05	0.001314	-0.23856	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	DENND1C	denn domain-containing protein 1c	-0.21578	2.99E-05	0.002576	-0.28936	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	DSG3	desmoglein-3	-0.235	5.19E-06	0.000746	-0.25127	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	ITGB4	integrin beta-4	-0.3273	1.23E-10	2.84E-07	-0.3346	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.22431	1.4E-05	0.001526	-0.27834	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.20934	5.18E-05	0.003767	-0.29174	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	LTB	lymphotoxin-beta	-0.18179	0.000457	0.015979	-0.27785	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	MAPK10	mitogen-activated protein kinase 10	-0.16933	0.001111	0.027933	-0.27145	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	PTAFR	platelet-activating factor receptor	-0.21688	2.71E-05	0.002407	-0.27523	IM	-0.18309	IM	-0.10679
K19540840	saracatinib	src inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.27973	4.84E-08	2.48E-05	-0.32068	IM	-0.18309	IM	-0.10679
K22134346	simvastatin	HMGCR inhibitor	ARHGAP31	rho gtpase-activating protein	-0.19459	0.00024	0.010527	-0.30771	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	ARMCX1	armadillo repeat-containing x-linked protein 1	-0.18048	0.000669	0.020287	-0.29267	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	CNRIP1	cb1 cannabinoid receptor-interacting protein 1	-0.16703	0.001662	0.035614	-0.24491	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	CORO2B	coronin-2b	-0.1836	0.000536	0.01768	-0.27781	M	0.067288	M	0.0435

K22134346	simvastatin	HMGCR inhibitor	CYBRD1	cytochrome b reductase 1	-0.17273	0.001139	0.028369	-0.26682	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	EPHA3	ephrin type-a receptor 3	-0.21598	4.39E-05	0.003355	-0.29345	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	EVC	ellis-van creveld syndrome protein	-0.19689	0.000201	0.009402	-0.26818	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	EVI2A	protein evi2a	-0.1743	0.001024	0.026557	-0.28479	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	EXTL2	exostosin-2-related	-0.18191	0.000605	0.019045	-0.28106	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	FYN	tyrosine-protein kinase fyn	-0.1676	0.001602	0.034813	-0.27314	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	IFFO1	intermediate filament family orphan 1	-0.15898	0.002779	0.048357	-0.27534	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	KANK2	kn motif and ankyrin repeat domain-containing protein 2	-0.22304	2.41E-05	0.002217	-0.26204	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	LPAR4	lysophosphatidic acid receptor 4	-0.22919	1.41E-05	0.001533	-0.29553	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	MOXD1	dbh-like monooxygenase protein 1	-0.19563	0.000222	0.010019	-0.3012	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	PRKD1		-0.20819	8.31E-05	0.005182	-0.26241	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.19184	0.000294	0.012037	-0.32304	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	SLC35F1	solute carrier family 35 member f1	-0.17887	0.000748	0.021763	-0.26588	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	SRPX	sushi repeat-containing protein srpx	-0.20612	9.81E-05	0.005797	-0.27523	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.20277	0.000128	0.006929	-0.29578	M	0.067288	M	0.0435
K22134346	simvastatin	HMGCR inhibitor	ZCCHC24		-0.18723	0.000413	0.01496	-0.28228	M	0.067288	M	0.0435
K23190681	AV-412	protein tyrosine kinase inhibitor	ADAM8	disintegrin and metalloproteinase domain-containing protein 8	-0.19505	0.000188	0.008987	-0.33616	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.30013	5.7E-09	5.07E-06	-0.38225	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	ARHGDIB	rho gdp-dissociation inhibitor 2	-0.24095	3.53E-06	0.000571	-0.30378	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	ARHGEF4	rho guanine nucleotide exchange factor 4	-0.23562	5.86E-06	0.000814	-0.28733	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	CLEC12A	c-type lectin domain family 12 member a	-0.18846	0.000311	0.012492	-0.26652	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	COL17A1	collagen alpha-1	-0.36548	7E-13	6.5E-09	-0.38565	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	CXCL16	c-x-c motif chemokine 16	-0.23921	4.17E-06	0.000637	-0.27224	IM	-0.09469	IM	-0.04654

K23190681	AV-412	protein tyrosine kinase inhibitor	CYP4B1	cytochrome p450 4b1	-0.2049	8.61E-05	0.005306	-0.29417	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.42353	3.45E-17	5.17E-12	-0.48092	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	DENND1C	denn domain-containing protein 1c	-0.30432	3.4E-09	3.42E-06	-0.30076	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	DSG3	desmoglein-3	-0.40941	4.61E-16	3.68E-11	-0.35145	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.30954	1.77E-09	2.1E-06	-0.38366	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.2356	5.87E-06	0.000815	-0.32561	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	IL23A	interleukin-23 subunit alpha	-0.18689	0.00035	0.013472	-0.24999	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	ITGB4	integrin beta-4	-0.30699	2.44E-09	2.7E-06	-0.38114	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	KRT14	keratin; type i cytoskeletal 14	-0.32808	1.57E-10	3.48E-07	-0.28432	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.35228	5.13E-12	2.72E-08	-0.36828	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.41511	1.64E-16	2.11E-11	-0.41276	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.40516	9.82E-16	5.2E-11	-0.4264	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	LGALS9	galectin-9	-0.21804	2.86E-05	0.002496	-0.28354	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.30804	2.14E-09	2.43E-06	-0.28807	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	PTAFR	platelet-activating factor receptor	-0.42507	2.58E-17	4.64E-12	-0.49078	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	PTK7	inactive tyrosine-protein kinase 7	-0.1563	0.002865	0.049234	-0.25171	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.29966	6.03E-09	5.3E-06	-0.36555	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	RASSF5	ras association domain-containing protein 5	-0.16831	0.001309	0.0308	-0.24321	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	S100A8	protein s100-a8	-0.25632	7.7E-07	0.000189	-0.34257	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	SH3BP1	bargin-related	-0.37018	3.36E-13	3.83E-09	-0.36164	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.19284	0.000223	0.010069	-0.26026	IM	-0.09469	IM	-0.04654

K23190681	AV-412	protein tyrosine kinase inhibitor	UNC13D	protein unc-13 homolog d	-0.17151	0.001052	0.026995	-0.31853	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	VAV1	proto-oncogene vav	-0.23139	8.68E-06	0.001085	-0.24926	IM	-0.09469	IM	-0.04654
K23190681	AV-412	protein tyrosine kinase inhibitor	XCL1	cytokine scm-1 beta-related	-0.22931	1.05E-05	0.001242	-0.28227	IM	-0.09469	IM	-0.04654
K23925186	oridonin	BCL inhibitor	DACT3	dapper homolog 3	-0.19512	0.000191	0.009082	-0.25452	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	FAM78A	protein fam78a	-0.18993	0.000284	0.01177	-0.29067	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	FMNL3	formin-like protein 3	-0.18322	0.000467	0.016206	-0.25822	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	LZTS2	zipper putative tumor suppressor 2-related	-0.17041	0.001153	0.028547	-0.25743	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	MEX3A	rna-binding protein mex3a	-0.18672	0.000361	0.013741	-0.24883	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	MYH10	myosin-10	-0.19038	0.000275	0.011509	-0.23849	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	PHC1	polyhomeotic-like protein 1	-0.18315	0.00047	0.016262	-0.25094	M	0.132126	M	0.182341
K23925186	oridonin	BCL inhibitor	PLPP7	inactive phospholipid phosphatase 7	-0.22048	2.37E-05	0.00219	-0.26422	M	0.132126	M	0.182341
K26603252	PD-153035	EGFR inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.25089	1.58E-06	0.000318	-0.3717	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.26685	3.1E-07	9.81E-05	-0.32904	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	COL17A1	collagen alpha-1	-0.29128	2.07E-08	1.32E-05	-0.41109	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.25839	7.44E-07	0.000185	-0.37765	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	CYP4B1	cytochrome p450 4b1	-0.16797	0.001446	0.032741	-0.28801	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.30983	2.21E-09	2.51E-06	-0.42316	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.31092	1.93E-09	2.23E-06	-0.42894	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.24765	2.17E-06	0.000399	-0.30233	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	DSG3	desmoglein-3	-0.35668	3.77E-12	2.15E-08	-0.34572	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.31466	1.21E-09	1.59E-06	-0.40356	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.22028	2.68E-05	0.002388	-0.30664	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	ITGB4	integrin beta-4	-0.34404	2.34E-11	8.31E-08	-0.42238	IM	-0.12324	IM	-0.03709

K26603252	PD-153035	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.35401	5.59E-12	2.92E-08	-0.34579	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.30703	3.13E-09	3.24E-06	-0.29342	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.34628	1.71E-11	6.71E-08	-0.35965	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.36061	2.1E-12	1.44E-08	-0.30522	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.34036	3.93E-11	1.22E-07	-0.46794	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.37993	1.05E-13	1.67E-09	-0.44809	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	S100A8	protein s100-a8	-0.17309	0.001024	0.026552	-0.32322	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	SH3BP1	bargin-related	-0.27535	1.24E-07	4.99E-05	-0.27597	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.18599	0.000411	0.014909	-0.26662	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.32407	3.57E-10	6.27E-07	-0.24719	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	UNC13D	protein unc-13 homolog d	-0.21	6.37E-05	0.004334	-0.26712	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	VSIR	v-type immunoglobulin domain-containing suppressor of t-cell activation	-0.18997	0.000307	0.012364	-0.24091	IM	-0.12324	IM	-0.03709
K26603252	PD-153035	EGFR inhibitor	ZMYND15	zinc finger mynd domain-containing protein 15	-0.2211	2.5E-05	0.002273	-0.25641	IM	-0.12324	IM	-0.03709
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	BCL2A1	bcl-2-related protein a1	-0.18098	0.000503	0.016968	-0.39482	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	CDH19	cadherin-19	-0.21375	3.74E-05	0.003006	-0.30692	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	CHL1	atp-dependent dna helicase ddx11-related	-0.27143	1.33E-07	5.25E-05	-0.34136	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	COL19A1	collagen alpha-1	-0.19727	0.000146	0.007566	-0.45596	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	DAAM2	dishevled-associated activator of morphogenesis 2	-0.19175	0.000224	0.010092	-0.39135	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	EDNRB	endothelin receptor type b	-0.24594	1.91E-06	0.000366	-0.4605	M	0.083765	M	0.246345

K26818574	BIX-01294	histone lysine methyltransferase inhibitor	FAM180B	protein fam180b	-0.21795	2.6E-05	0.002336	-0.48481	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.17993	0.000543	0.017808	-0.30448	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.20657	6.85E-05	0.004551	-0.2798	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	FCRLA	fc receptor-like a	-0.31111	1.18E-09	1.57E-06	-0.4011	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	GAS7	growth arrest-specific protein 7	-0.20989	5.19E-05	0.003772	-0.42807	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	GYPC	glycophorin-c	-0.18523	0.000367	0.013881	-0.30433	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.18052	0.00052	0.017326	-0.33563	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	IL16	pro-interleukin-16	-0.27842	6.1E-08	2.92E-05	-0.4846	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	IRF4	interferon regulatory factor 4	-0.2269	1.17E-05	0.00134	-0.43689	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	ITIH5	inter-alpha-trypsin inhibitor heavy chain h5	-0.17979	0.000548	0.017922	-0.26924	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	KCNJ10	atp-sensitive inward rectifier potassium channel 10	-0.16171	0.001912	0.038705	-0.27546	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	LPXN	leupaxin	-0.16953	0.001131	0.028245	-0.25428	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	MIA	melanoma-derived growth regulatory protein	-0.20089	0.000109	0.006216	-0.33434	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.15854	0.002351	0.043822	-0.26243	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	P2RX7	p2x purinoceptor 7	-0.21415	3.61E-05	0.002939	-0.27448	M	0.083765	M	0.246345

K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PDZRN3	e3 ubiquitin-protein ligase pdzrn3	-0.18642	0.000336	0.013121	-0.2683	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PKNOX2	homeobox protein pknox2	-0.20258	9.5E-05	0.005672	-0.35864	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PLEKHO2	pleckstrin homology domain-containing family o member 2	-0.1935	0.000196	0.009229	-0.3448	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PLP1	myelin proteolipid protein	-0.265	2.68E-07	8.82E-05	-0.4139	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PMP2	myelin p2 protein	-0.30337	3.14E-09	3.24E-06	-0.35054	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.24819	1.53E-06	0.000311	-0.48186	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.1905	0.000247	0.010735	-0.43127	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.22446	1.46E-05	0.00157	-0.34455	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	SCML4	sex comb on midleg-like protein 4	-0.1827	0.000443	0.015658	-0.29749	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	SGCD	delta-sarcoglycan	-0.19606	0.00016	0.008056	-0.39099	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	SHC4	shc-transforming protein 4	-0.21965	2.24E-05	0.002108	-0.34777	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	SORBS1	sorbin and sh3 domain-containing protein 1	-0.15877	0.002316	0.043413	-0.36063	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.22926	9.41E-06	0.001151	-0.30163	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2;8-sialyltransferase	-0.19011	0.000254	0.010944	-0.27717	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	TAMALIN	protein tamalin	-0.20005	0.000117	0.006516	-0.37086	M	0.083765	M	0.246345

K26818574	BIX-01294	histone lysine methyltransferase inhibitor	TMEM229B	transmembrane protein 229b	-0.17272	0.000907	0.024562	-0.29055	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.1858	0.000352	0.013517	-0.41205	M	0.083765	M	0.246345
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	WFDC1	wap four-disulfide core domain protein 1	-0.22462	1.44E-05	0.001556	-0.35978	M	0.083765	M	0.246345
K28061410	beta-lapachone	topoisomerase inhibitor	APOLD1	apolipoprotein l domain-containing protein 1	-0.2156	4.53E-05	0.00343	-0.24277	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.23539	8.06E-06	0.001029	-0.24866	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	FAM180B	protein fam180b	-0.26199	6.19E-07	0.000162	-0.27998	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	GAS7	growth arrest-specific protein 7	-0.26458	4.75E-07	0.000133	-0.31098	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.20939	7.54E-05	0.00486	-0.2616	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	IL16	pro-interleukin-16	-0.261	6.85E-07	0.000174	-0.26434	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	IRF4	interferon regulatory factor 4	-0.27181	2.23E-07	7.65E-05	-0.26084	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	ITK	tyrosine-protein kinase itk/tsk	-0.18526	0.000476	0.016405	-0.24098	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	LZTS1		-0.25159	1.75E-06	0.000342	-0.26685	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	PKNOX2	homeobox protein pknox2	-0.23233	1.06E-05	0.001255	-0.28919	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.22947	1.37E-05	0.001505	-0.29461	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	SHC4	shc-transforming protein 4	-0.18615	0.000447	0.015745	-0.24831	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	ST6GALNAC3	alpha-n-acetylgalactosaminide alpha-2;6-sialyltransferase 3	-0.21788	3.74E-05	0.003009	-0.25187	M	0.121653	M	0.182082
K28061410	beta-lapachone	topoisomerase inhibitor	TAMALIN	protein tamalin	-0.17178	0.001214	0.029433	-0.26574	M	0.121653	M	0.182082
K28824103	genipin	choleretic agent	ABI2	abl interactor 2	-0.17755	0.000942	0.025176	-0.25554	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.18554	0.000542	0.017803	-0.27342	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	ADGRB2	adhesion g protein-coupled receptor b2	-0.18503	0.000562	0.018194	-0.27272	M	0.094785	M	0.105229

K28824103	genipin	choleretic agent	CAND2	cullin-associated nedd8-dissociated protein 2	-0.20781	0.000103	0.005996	-0.27123	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	CBX1	chromobox protein homolog 1	-0.25264	2.08E-06	0.000387	-0.25015	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	CHD3	chromodomain-helicase-dna-binding protein 3	-0.17169	0.001391	0.031984	-0.24417	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	FAM171A2	protein fam171a2	-0.22398	2.76E-05	0.002434	-0.25384	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	FOXO3B	forkhead box protein o3b-related	-0.19201	0.000341	0.013251	-0.27763	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	MPP2	forkhead box protein m1	-0.18453	0.000582	0.018604	-0.32854	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	MRC2	c-type mannose receptor 2	-0.21017	8.57E-05	0.005291	-0.26049	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	NLGN2	neuroligin-2	-0.21373	6.44E-05	0.004368	-0.25824	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	PALM	paralemmin-1	-0.17135	0.001422	0.032415	-0.24524	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	PDZD4	pdz domain-containing protein 4	-0.23529	1.03E-05	0.001227	-0.24402	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	RBPMS2	rna-binding protein with multiple splicing 2	-0.22239	3.16E-05	0.002676	-0.3638	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	SMO	smoothened homolog	-0.21454	6.04E-05	0.004173	-0.27256	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	TUB	tubby protein homolog	-0.22462	2.61E-05	0.002346	-0.25911	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	USP22	ubiquitin carboxyl-terminal hydrolase 22	-0.17164	0.001396	0.032059	-0.25991	M	0.094785	M	0.105229
K28824103	genipin	choleretic agent	VASH1	tubulinyl-tyr carboxypeptidase 1	-0.26042	9.71E-07	0.000225	-0.28016	M	0.094785	M	0.105229
K30159788	RSV604	RSV replication inhibitor	FGFR1	fibroblast growth factor receptor 1	-0.16628	0.001799	0.037375	-0.26638	MSL	-0.0004	MSL	0.050206
K30933884	UNBS-5162	CC chemokine receptor antagonist	ABI2	abl interactor 2	-0.1664	0.001399	0.032097	-0.28321	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.19943	0.000123	0.006736	-0.27114	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	DLX6	homeobox protein dlx-6	-0.19115	0.000235	0.010384	-0.25188	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	EMILIN3	emilin-3	-0.18183	0.000473	0.016326	-0.23795	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	FAM171A2	protein fam171a2	-0.27943	5.44E-08	2.69E-05	-0.27281	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	FOXO3B	forkhead box protein o3b-related	-0.2549	7.74E-07	0.00019	-0.25677	M	0.098439	M	0.091475

K30933884	UNBS-5162	CC chemokine receptor antagonist	GALNT17	polypeptide n-acetylgalactosaminyltransfer ase-like 6	-0.21945	2.28E-05	0.002135	-0.3209	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	KCNJ4	inward rectifier potassium channel 4	-0.19046	0.000248	0.01076	-0.23833	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	MEX3A	rna-binding protein mex3a	-0.29311	1.1E-08	8.3E-06	-0.24131	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	MPP2	forkhead box protein m1	-0.1761	0.000715	0.021151	-0.28776	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	MSI1	rna-binding protein musashi homolog 1	-0.21573	3.15E-05	0.002674	-0.34931	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	NEXMIF	neurite extension and migration factor	-0.15635	0.002705	0.047585	-0.29824	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.16784	0.001269	0.03025	-0.2576	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	RBPMS2	rna-binding protein with multiple splicing 2	-0.19022	0.000252	0.010882	-0.25586	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	RCOR2	rest corepressor 2	-0.23613	4.96E-06	0.000722	-0.25441	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	SALL2	sal-like protein 2	-0.21383	3.71E-05	0.002992	-0.30324	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	SMO	smoothened homolog	-0.21816	2.55E-05	0.002307	-0.25619	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	TMPO	lamina-associated polypeptide 2; isoform alpha	-0.19738	0.000144	0.00752	-0.25031	M	0.098439	M	0.091475
K30933884	UNBS-5162	CC chemokine receptor antagonist	ZC3H12B	ribonuclease zc3h12b-related	-0.16416	0.001625	0.035123	-0.27218	M	0.098439	M	0.091475
K31698212	icotinib	EGFR inhibitor	APOL1	apolipoprotein l1	-0.18094	0.000487	0.016629	-0.24361	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.17078	0.001005	0.026235	-0.31509	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	ITGB4	integrin beta-4	-0.21779	2.5E-05	0.002277	-0.31123	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.19422	0.000178	0.008644	-0.24565	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	NMI	n-myc-interactor	-0.22911	9.03E-06	0.001118	-0.27643	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	NTN4	netrin-4	-0.16545	0.001447	0.032749	-0.24283	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.18871	0.000272	0.011433	-0.3502	IM	-0.13826	IM	-0.10753
K31698212	icotinib	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.18482	0.000365	0.013828	-0.28189	IM	-0.13826	IM	-0.10753

K31698212	icotinib	EGFR inhibitor	VSIR	v-type immunoglobulin domain-containing suppressor of t-cell activation	-0.16724	0.001282	0.030424	-0.27989	IM	-0.13826	IM	-0.10753
K31866293	TAK-632	RAF inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.22412	1.5E-05	0.001605	-0.27406	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.23617	4.93E-06	0.00072	-0.26144	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	C3orf70	upf0524 protein c3orf70	-0.17213	0.000945	0.025219	-0.34983	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	CDH19	cadherin-19	-0.25999	4.56E-07	0.000129	-0.28578	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	COL19A1	collagen alpha-1	-0.24146	2.97E-06	0.000501	-0.37648	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	COL9A3	collagen alpha-3	-0.20202	9.95E-05	0.005851	-0.27006	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.25042	1.22E-06	0.000265	-0.31554	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.18718	0.000318	0.012649	-0.24656	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	CYGB	cytoglobin	-0.21969	2.23E-05	0.002102	-0.24697	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	DAAM2	dishevelled-associated activator of morphogenesis 2	-0.17349	0.000859	0.023734	-0.34372	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	EDNRB	endothelin receptor type b	-0.27431	9.68E-08	4.12E-05	-0.30546	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	FAM180B	protein fam180b	-0.19812	0.000136	0.007225	-0.30667	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.20097	0.000108	0.006187	-0.27229	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.25496	7.7E-07	0.000189	-0.28451	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	FCRLA	fc receptor-like a	-0.25098	1.15E-06	0.000255	-0.36943	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	GAS7	growth arrest-specific protein 7	-0.22745	1.11E-05	0.001292	-0.37157	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	GNG2	guanine nucleotide-binding protein g	-0.23746	4.37E-06	0.000659	-0.25302	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	GPR55	g-protein coupled receptor 55	-0.18214	0.000462	0.016073	-0.2411	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	GSN	gelsolin	-0.16453	0.001586	0.034612	-0.28152	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.23792	4.18E-06	0.000637	-0.24854	M	0.084888	M	0.20887

K31866293	TAK-632	RAF inhibitor	IL16	pro-interleukin-16	-0.2221	1.8E-05	0.001814	-0.40428	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	IRF4	interferon regulatory factor 4	-0.25383	8.64E-07	0.000206	-0.3306	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	ITGA9	integrin alpha-9	-0.20334	8.94E-05	0.005434	-0.24189	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	LZTS1		-0.16699	0.001344	0.031303	-0.31698	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	MCC	colorectal mutant cancer protein	-0.17802	0.000623	0.019405	-0.23874	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	MEF2C	myocyte-specific enhancer factor 2c	-0.16874	0.001193	0.029125	-0.2599	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	MIA	melanoma-derived growth regulatory protein	-0.21401	3.66E-05	0.002959	-0.32825	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	NES	nestin	-0.23999	3.42E-06	0.000556	-0.27216	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	NFATC2	nuclear factor of activated t-cells; cytoplasmic 2	-0.21452	3.5E-05	0.002875	-0.3235	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.24743	1.65E-06	0.000328	-0.29319	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	PKNOX2	homeobox protein pknox2	-0.21417	3.61E-05	0.002936	-0.26336	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	PLP1	myelin proteolipid protein	-0.27768	6.64E-08	3.11E-05	-0.3682	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	PMP2	myelin p2 protein	-0.24436	2.24E-06	0.000407	-0.33352	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.29656	7.26E-09	6.1E-06	-0.35336	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.19088	0.00024	0.010525	-0.27166	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	RGS1	regulator of g-protein signaling 1	-0.25298	9.43E-07	0.000219	-0.27287	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	SCML4	sex comb on midleg-like protein 4	-0.21216	4.28E-05	0.003297	-0.26235	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	SGCD	delta-sarcoglycan	-0.19728	0.000145	0.007559	-0.34988	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	SOX5	transcription factor sox-5	-0.18047	0.000522	0.017376	-0.24658	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	SRPX	sushi repeat-containing protein srpx	-0.21441	3.53E-05	0.002893	-0.24491	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	ST6GALNAC3	alpha-n-acetylgalactosaminide alpha-2,6-sialyltransferase 3	-0.20411	8.39E-05	0.005213	-0.28039	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	TAMALIN	protein tamalin	-0.24933	1.36E-06	0.000286	-0.27589	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	TIMP3	metalloproteinase inhibitor 3	-0.17239	0.000928	0.024946	-0.3191	M	0.084888	M	0.20887

K31866293	TAK-632	RAF inhibitor	TMEM229B	transmembrane protein 229b	-0.18695	0.000323	0.012799	-0.32241	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	TNFRSF14	tumor necrosis factor receptor superfamily member 14	-0.2052	7.67E-05	0.004914	-0.28456	M	0.084888	M	0.20887
K31866293	TAK-632	RAF inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.28492	2.9E-08	1.68E-05	-0.28755	M	0.084888	M	0.20887
K33882852	ZK-93423	benzodiazepine receptor agonist	KBTBD6	kelch repeat and btb domain-containing protein 6	-0.17118	0.001129	0.028226	-0.24466	M	0.10975	M	0.176686
K37561857	zardaverine	phosphodiesterase inhibitor	ABCA8	atp-binding cassette sub-family a member 8	-0.19836	0.000162	0.008113	-0.32422	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ANTXR1	anthrax toxin receptor 1	-0.19276	0.000249	0.010789	-0.30004	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ARHGAP31	rho gtpase-activating protein 31	-0.20084	0.000133	0.007118	-0.24472	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ATOH8	protein atonal homolog 8	-0.16205	0.002131	0.041347	-0.25099	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	CALD1	caldesmon	-0.18504	0.000441	0.015609	-0.29655	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	CNRIP1	cb1 cannabinoid receptor-interacting protein 1	-0.17643	0.000814	0.022944	-0.24266	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	CPQ	carboxypeptidase q	-0.17899	0.00068	0.020495	-0.29959	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.16638	0.001607	0.034882	-0.30142	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	DAAM2	dishevled-associated activator of morphogenesis 2	-0.20754	7.79E-05	0.004966	-0.26364	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	DSTYK	dual serine/threonine and tyrosine protein kinase	-0.18113	0.000584	0.018637	-0.32209	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ENOX1	ecto-nox disulfide-thiol exchanger 1	-0.16359	0.001929	0.038927	-0.25369	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	FBXL7	f-box/lrr-repeat protein 7	-0.20876	7.05E-05	0.004644	-0.27171	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	FERMT2	fermitin family homolog 2	-0.16566	0.001685	0.035933	-0.2411	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	GPC6	glypican-6	-0.18707	0.00038	0.014178	-0.24855	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	GUCY1A2	guanylate cyclase soluble subunit alpha-2	-0.20046	0.000137	0.007269	-0.29039	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	HTRA1	serine protease htra1	-0.22933	1.21E-05	0.001372	-0.25932	M	0.178243	MSL/M	0.169947

K37561857	zardaverine	phosphodiesterase inhibitor	JAZF1	juxtaposed with another zinc finger protein 1	-0.16909	0.001343	0.031285	-0.27681	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	KIRREL1	kin of irre-like protein 1	-0.22012	2.72E-05	0.002408	-0.28477	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	LAMA4	laminin subunit alpha-4	-0.19769	0.00017	0.008407	-0.29128	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	MMP16	matrix metalloproteinase-16	-0.17737	0.000762	0.022009	-0.26196	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	PCDHB7	protocadherin beta-7	-0.20994	6.41E-05	0.004352	-0.29052	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	PDE1C	calcium/calmodulin-dependent 3′,5′-cyclic nucleotide phosphodiesterase 1c	-0.19619	0.000191	0.009081	-0.31468	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	PDE7B	camp-specific 3′,5′-cyclic phosphodiesterase 7b	-0.17821	0.000718	0.021216	-0.26066	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	PYGO1	pygopus homolog 1	-0.18995	0.000307	0.012374	-0.24375	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	RASSF8	ras association domain-containing protein 8	-0.19687	0.000182	0.00877	-0.24749	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	RECK	reversion-inducing cysteine-rich protein with kazal motifs	-0.19612	0.000192	0.00911	-0.25912	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.22677	1.52E-05	0.001614	-0.27811	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SH3PXD2B	sh3 and px domain-containing protein 2b	-0.20235	0.000118	0.006577	-0.26621	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SHC4	shc-transforming protein 4	-0.21121	5.77E-05	0.004046	-0.32295	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SHISA4	protein shisa-4	-0.16891	0.001358	0.031518	-0.25725	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SMIM10	small integral membrane protein 10	-0.16019	0.002399	0.044354	-0.24592	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SPARC	sparc	-0.20897	6.93E-05	0.004588	-0.2752	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SRPX	sushi repeat-containing protein srpx	-0.19884	0.000156	0.007908	-0.26039	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ST3GAL2	cmp-n-acetylneuraminate-beta-galactosamide-alpha-2;3-sialyltransferase 2	-0.17048	0.001222	0.029555	-0.24425	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.21693	3.57E-05	0.002914	-0.24653	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	TMTC1	protein o-mannosyl-transferase tmtc1	-0.15846	0.002677	0.047273	-0.32165	M	0.178243	MSL/M	0.169947

K37561857	zardaverine	phosphodiesterase inhibitor	TUB	tubby protein homolog	-0.22575	1.66E-05	0.001718	-0.29453	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ZCCHC24		-0.17043	0.001227	0.029623	-0.29506	M	0.178243	MSL/M	0.169947
K37561857	zardaverine	phosphodiesterase inhibitor	ZEB2	zinc finger e-box-binding homeobox 2	-0.19207	0.000262	0.011141	-0.25775	M	0.178243	MSL/M	0.169947
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.22798	1.03E-05	0.001224	-0.23757	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	GASK1B	golgi-associated kinase 1b	-0.24597	1.85E-06	0.000357	-0.25533	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	GHR	growth hormone receptor	-0.26955	1.58E-07	5.93E-05	-0.24933	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	HMCN1	hemicentin-1	-0.3493	5.7E-12	2.97E-08	-0.24951	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	IL16	pro-interleukin-16	-0.28479	2.81E-08	1.65E-05	-0.30037	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	IRF4	interferon regulatory factor 4	-0.2899	1.54E-08	1.07E-05	-0.25946	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	PARD6G	partitioning defective 6 homolog gamma	-0.27305	1.07E-07	4.47E-05	-0.26637	M	0.256196	M	0.168251
K40109029	SB-505124	ALK tyrosine kinase receptor inhibitor	TMEM229B	transmembrane protein 229b	-0.16465	0.00155	0.034145	-0.25527	M	0.256196	M	0.168251
K46386702	ARRY-334543	EGFR inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.21787	2.75E-05	0.00243	-0.35167	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.27871	6.42E-08	3.04E-05	-0.27596	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	ARHGEF4	rho guanine nucleotide exchange factor 4	-0.18456	0.000401	0.01467	-0.24294	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	BCL2L14	apoptosis facilitator bcl-2-like protein 14	-0.18512	0.000385	0.014282	-0.2448	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	COL17A1	collagen alpha-1	-0.2911	1.53E-08	1.06E-05	-0.36549	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.25673	6.88E-07	0.000175	-0.38672	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	CYP4B1	cytochrome p450 4b1	-0.20516	8.06E-05	0.005075	-0.33476	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.33215	7.99E-11	2.05E-07	-0.38968	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.28544	2.97E-08	1.71E-05	-0.40436	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.2154	3.41E-05	0.002822	-0.28939	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	DSG3	desmoglein-3	-0.3574	2.08E-12	1.44E-08	-0.30164	IM	-0.05992	IM	-0.03109

K46386702	ARRY-334543	EGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.28765	2.3E-08	1.43E-05	-0.38187	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.17983	0.000566	0.018269	-0.35709	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	ITGB4	integrin beta-4	-0.3474	9.18E-12	4.18E-08	-0.43913	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.36969	3.13E-13	3.61E-09	-0.34942	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.33817	3.45E-11	1.12E-07	-0.32262	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.33128	9.02E-11	2.25E-07	-0.26495	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	LGALS9	galectin-9	-0.18266	0.000461	0.016061	-0.30803	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.31234	1.12E-09	1.51E-06	-0.35547	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.33877	3.17E-11	1.04E-07	-0.4259	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.33498	5.4E-11	1.51E-07	-0.38814	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	RASGEF1B	ras-gef domain-containing family member 1b	-0.15931	0.0023	0.043244	-0.24753	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	S100A8	protein s100-a8	-0.18814	0.000307	0.012371	-0.2876	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	SH3BP1	bargin-related	-0.28775	2.28E-08	1.41E-05	-0.30924	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.17104	0.001052	0.026995	-0.2414	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	TEAD3	transcriptional enhancer factor tef-5	-0.23145	8.15E-06	0.001036	-0.26729	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.25726	6.52E-07	0.000168	-0.28575	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	TRAF3IP3	traf3-interacting jnk-activating modulator	-0.17141	0.001026	0.026579	-0.26103	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	UNC13D	protein unc-13 homolog d	-0.20271	9.83E-05	0.005808	-0.29889	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	VIPR1	vasoactive intestinal polypeptide receptor 1	-0.16628	0.001454	0.032847	-0.26419	IM	-0.05992	IM	-0.03109
K46386702	ARRY-334543	EGFR inhibitor	ZMYND15	zinc finger mynd domain-containing protein 15	-0.23897	4.02E-06	0.000622	-0.26625	IM	-0.05992	IM	-0.03109
K49294207	BIBU-1361	EGFR inhibitor	COL17A1	collagen alpha-1	-0.24453	2.67E-06	0.000463	-0.3684	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.20584	8.35E-05	0.005199	-0.36341	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-	-0.27615	1.01E-07	4.26E-05	-0.40028	IM	-0.06618	IM	-0.00947

K49294207	BIBU-1361	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.27792	8.29E-08	3.67E-05	-0.38121	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.19684	0.000171	0.008425	-0.24489	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	DSG3	desmoglein-3	-0.28748	2.8E-08	1.65E-05	-0.33781	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.23197	8.72E-06	0.001089	-0.31506	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.17298	0.000983	0.02586	-0.34629	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	ITGB4	integrin beta-4	-0.30544	3.28E-09	3.33E-06	-0.39282	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.26326	4.04E-07	0.000119	-0.42928	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.27269	1.47E-07	5.65E-05	-0.31196	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.25941	6.02E-07	0.000159	-0.25585	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.26692	2.74E-07	8.96E-05	-0.33857	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.28153	5.53E-08	2.72E-05	-0.38521	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.32344	3.27E-10	5.85E-07	-0.40666	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	SH3BP1	bargin-related	-0.1607	0.002225	0.042431	-0.24329	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.18684	0.000365	0.013828	-0.25174	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.2681	2.42E-07	8.16E-05	-0.25405	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	UNC13D	protein unc-13 homolog d	-0.1927	0.000235	0.010393	-0.26505	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	VSIR	v-type immunoglobulin domain-containing suppressor of t-cell activation	-0.16145	0.00212	0.041224	-0.24964	IM	-0.06618	IM	-0.00947
K49294207	BIBU-1361	EGFR inhibitor	ZMYND15	zinc finger mynd domain-containing protein 15	-0.17407	0.000911	0.024644	-0.29204	IM	-0.06618	IM	-0.00947
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src	ANKRD33B	ankyrin repeat domain-containing protein 33b	-0.27464	1.24E-07	4.98E-05	-0.29073	IM	-0.17261	IM	-0.06188

		inhibitor; tyrosine kinase inhibitor									
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	APOL1	apolipoprotein l1	-0.2592	6.38E-07	0.000165	-0.25243	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	BIRC3	baculoviral iap repeat-containing protein 3	-0.23852	4.88E-06	0.000715	-0.27806	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	C15orf48	normal mucosa of esophagus-specific gene 1 protein	-0.16281	0.00197	0.039424	-0.27745	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	CATSPER 1	cation channel sperm-associated protein 1	-0.1617	0.002117	0.041188	-0.27935	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	CLEC4E	c-type lectin domain family 4 member e	-0.2357	6.36E-06	0.000866	-0.26912	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	CLIP4	cap-gly domain-containing linker protein 4	-0.20482	9.28E-05	0.005573	-0.26572	IM	-0.17261	IM	-0.06188

K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	DRAM1	dna damage-regulated autophagy modulator protein 1	-0.16332	0.001905	0.038619	-0.28159	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	IGFBP7	insulin-like growth factor-binding protein 7	-0.21189	5.19E-05	0.003772	-0.24301	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	IL15RA	interleukin-15 receptor subunit alpha	-0.18942	0.000307	0.012374	-0.23909	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	IL32		-0.20068	0.000129	0.006977	-0.2635	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	LTB	lymphotoxin-beta	-0.16377	0.00185	0.037996	-0.2851	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	RAC2	ras-related c3 botulinum toxin substrate 2	-0.17604	0.000808	0.022845	-0.26127	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor;	SORCS2	vps10 domain-containing receptor sorcs2	-0.18499	0.000426	0.015275	-0.29236	IM	-0.17261	IM	-0.06188

		PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor										
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	SYTL3	synaptotagmin-like protein 3	-0.20501	9.13E-05	0.005515	-0.30285	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	TNF	tumor necrosis factor	-0.30221	5.12E-09	4.68E-06	-0.34193	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	TNFAIP3	tumor necrosis factor alpha-induced protein 3	-0.21998	2.61E-05	0.002344	-0.25472	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	TNFAIP8	tumor necrosis factor alpha-induced protein 8	-0.22123	2.34E-05	0.002171	-0.24852	IM	-0.17261	IM	-0.06188
K49328571	dasatinib	Bcr-Abl kinase inhibitor; ephrin inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; src inhibitor; tyrosine kinase inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.23745	5.4E-06	0.000768	-0.24386	IM	-0.17261	IM	-0.06188
K52256627	chlorhexidine	membrane integrity inhibitor	DKK2	dickkopf-related protein 2	-0.18693	0.000342	0.01328	-0.24772	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	DLX6	homeobox protein dlx-6	-0.16972	0.00117	0.028791	-0.23759	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	GPC3	glypican-3	-0.18758	0.000326	0.012879	-0.26201	M	0.14564	M	0.086625

K52256627	chlorhexidine	membrane integrity inhibitor	PDZD4	pdz domain-containing protein 4	-0.27835	6.97E-08	3.24E-05	-0.27238	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	PLPP7	inactive phospholipid phosphatase 7	-0.2006	0.000119	0.006608	-0.25559	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	RBPMS2	rna-binding protein with multiple splicing 2	-0.2576	6.52E-07	0.000168	-0.26519	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	SCARF2	scavenger receptor class f member 2	-0.21162	4.82E-05	0.003581	-0.27678	M	0.14564	M	0.086625
K52256627	chlorhexidine	membrane integrity inhibitor	SMO	smoothened homolog	-0.23997	3.76E-06	0.000595	-0.26163	M	0.14564	M	0.086625
K54395039	PR-619	DUB inhibitor	ANXA6	annexin a6	-0.17686	0.000665	0.020214	-0.29594	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	ATP8B2	phospholipid-transporting atpase id	-0.16357	0.001666	0.035668	-0.24748	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	C3orf18	similar to riken cdna 6430571113 gene; similar to g20 protein	-0.22346	1.55E-05	0.001641	-0.24104	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	DLG4	disks large homolog 4-related	-0.15763	0.002458	0.044954	-0.30239	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	FBXL7	f-box/lrr-repeat protein 7	-0.21952	2.21E-05	0.002085	-0.23699	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	FMNL3	formin-like protein 3	-0.23918	3.59E-06	0.000577	-0.24778	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	FOXO3B	forkhead box protein o3b-related	-0.15492	0.002923	0.049814	-0.25412	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	PEAK1	inactive tyrosine-protein kinase peak1	-0.18788	0.000295	0.012059	-0.28406	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	REEP2	receptor expression-enhancing protein 2	-0.16837	0.001205	0.029304	-0.25182	M	0.099296	M	0.056745
K54395039	PR-619	DUB inhibitor	SHANK1	sh3 and multiple ankyrin repeat domains protein 1	-0.19641	0.000153	0.00781	-0.30708	M	0.099296	M	0.056745
K54634444	artesunate	DNA synthesis inhibitor	EMILIN3	emilin-3	-0.18551	0.000347	0.013375	-0.27206	M	0.132469	M	0.077482
K54634444	artesunate	DNA synthesis inhibitor	MSI1	rna-binding protein musashi homolog 1	-0.16232	0.001784	0.037183	-0.27116	M	0.132469	M	0.077482
K54634444	artesunate	DNA synthesis inhibitor	PIANP	plrr alpha-associated neural protein	-0.20638	6.64E-05	0.004457	-0.25949	M	0.132469	M	0.077482
K58529924	ONC201	AKT inhibitor; MAP kinase inhibitor	DIRAS1	gtp-binding protein di-ras1	-0.16074	0.002488	0.045255	-0.25377	M	0.050772	M	0.104631
K58529924	ONC201	AKT inhibitor; MAP kinase inhibitor	DVL2	segment polarity protein dishevelled homolog dvl-2	-0.20955	7.44E-05	0.004816	-0.25991	M	0.050772	M	0.104631
K58529924	ONC201	AKT inhibitor; MAP kinase inhibitor	MLLT1	protein enl	-0.16029	0.00256	0.046038	-0.28115	M	0.050772	M	0.104631
K60130390	UNC0642	histone lysine methyltransferase inhibitor	ISG15	ubiquitin-like protein isg15	-0.17866	0.000786	0.022451	-0.295	IM	-0.0704	IM	-0.1219

K60443845	chlormidazole	fungal lanosterol demethylase inhibitor	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.19749	0.000192	0.00911	-0.24658	M	0.20157	M	0.161226
K60443845	chlormidazole	fungal lanosterol demethylase inhibitor	MPP2	forkhead box protein m1	-0.20114	0.000145	0.007549	-0.26951	M	0.20157	M	0.161226
K60443845	chlormidazole	fungal lanosterol demethylase inhibitor	RCOR2	rest corepressor 2	-0.1723	0.001172	0.028828	-0.34902	M	0.20157	M	0.161226
K62200014	anagrelide	phosphodiesterase inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.17003	0.00124	0.029809	-0.27496	M	0.152247	M	0.254063
K62200014	anagrelide	phosphodiesterase inhibitor	FBXL7	f-box/lrr-repeat protein 7	-0.24722	2.19E-06	0.000401	-0.25199	M	0.152247	M	0.254063
K62200014	anagrelide	phosphodiesterase inhibitor	GYPC	glycophorin-c	-0.20748	7.65E-05	0.004905	-0.26615	M	0.152247	M	0.254063
K62200014	anagrelide	phosphodiesterase inhibitor	PIP4K2B	phosphatidylinositol 5-phosphate 4-kinase type-2 beta	-0.16979	0.001261	0.03013	-0.25046	M	0.152247	M	0.254063
K62200014	anagrelide	phosphodiesterase inhibitor	PYGO1	pygopus homolog 1	-0.16124	0.002213	0.042288	-0.24629	M	0.152247	M	0.254063
K62213621	dihydroartemisinin	antimalarial agent	ACTR3B	actin-related protein 3b-related	-0.18073	0.00056	0.018138	-0.26955	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	EMILIN3	emilin-3	-0.18969	0.00029	0.011906	-0.25533	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	FAM171A2	protein fam171a2	-0.19222	0.000239	0.010504	-0.2432	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	GALNT17	polypeptide n-acetylgalactosaminyltransferase-like 6	-0.18095	0.000551	0.017968	-0.2462	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	KCNH2	potassium voltage-gated channel subfamily h member 2	-0.19548	0.000186	0.008907	-0.25898	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	MEX3A	rna-binding protein mex3a	-0.23019	9.97E-06	0.001196	-0.31173	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	MPP2	forkhead box protein m1	-0.2072	7.3E-05	0.004756	-0.2677	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	MSI1	rna-binding protein musashi homolog 1	-0.21692	3.23E-05	0.002717	-0.40243	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	NYNRIN	protein nynrin	-0.17219	0.001021	0.026494	-0.3429	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	PIANP	plrl alpha-associated neural protein	-0.22657	1.38E-05	0.001512	-0.25594	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	RASL10B	ras-like protein family member 10b	-0.18815	0.000325	0.012846	-0.24285	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	RCOR2	rest corepressor 2	-0.19911	0.00014	0.007362	-0.32446	M	0.185453	M	0.134506

K62213621	dihydroartemisinin	antimalarial agent	SALL2	sal-like protein 2	-0.18409	0.000439	0.015554	-0.32241	M	0.185453	M	0.134506
K62213621	dihydroartemisinin	antimalarial agent	SYPL2	synaptophysin-like protein 2	-0.20391	9.54E-05	0.005686	-0.26159	M	0.185453	M	0.134506
K64052750	gefitinib	EGFR inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.23253	8.53E-06	0.00107	-0.39281	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.20112	0.000125	0.006815	-0.293	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	ARHGAP30	rho gtpase-activating protein 30	-0.16656	0.00154	0.034009	-0.34284	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	ARHGDIB	rho gdp-dissociation inhibitor 2	-0.1575	0.002767	0.048233	-0.30282	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	BCL2L14	apoptosis facilitator bcl-2-like protein 14	-0.19144	0.000264	0.011196	-0.24638	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	CLEC12A	c-type lectin domain family 12 member a	-0.20702	7.76E-05	0.004951	-0.24566	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	CLEC7A	c-type lectin domain family 7 member a	-0.24809	1.95E-06	0.000371	-0.24173	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	CLIC5	chloride intracellular channel protein 5	-0.18933	0.000309	0.012435	-0.25116	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	COL17A1	collagen alpha-1	-0.30786	2.55E-09	2.79E-06	-0.44664	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.26687	2.86E-07	9.23E-05	-0.3692	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	CYP4B1	cytochrome p450 4b1	-0.1937	0.000222	0.010038	-0.42112	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.30164	5.49E-09	4.93E-06	-0.44278	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.29433	1.32E-08	9.53E-06	-0.47596	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.21974	2.66E-05	0.002379	-0.31211	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	DSG3	desmoglein-3	-0.32232	4.01E-10	6.84E-07	-0.33991	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.30658	2.99E-09	3.13E-06	-0.42752	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.16146	0.00215	0.041575	-0.41121	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	ITGB4	integrin beta-4	-0.30107	5.88E-09	5.19E-06	-0.48548	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	KRT14	keratin; type i cytoskeletal 14	-0.30795	2.52E-09	2.77E-06	-0.29793	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.36143	1.61E-12	1.17E-08	-0.42779	IM	-0.06642	IM	-0.05639

K64052750	gefitinib	EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.31231	1.46E-09	1.85E-06	-0.38749	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.31631	8.77E-10	1.26E-06	-0.38115	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.32608	2.44E-10	4.72E-07	-0.40871	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.29641	1.03E-08	7.91E-06	-0.49763	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.35966	2.11E-12	1.44E-08	-0.47022	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	RASGEF1B	ras-gef domain-containing family member 1b	-0.1924	0.000245	0.010697	-0.25038	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	S100A8	protein s100-a8	-0.22101	2.39E-05	0.0022	-0.32493	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.18156	0.000546	0.017889	-0.29971	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	TEAD3	transcriptional enhancer factor tef-5	-0.20896	6.62E-05	0.004445	-0.29987	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.25786	7.32E-07	0.000183	-0.28333	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	UNC13D	protein unc-13 homolog d	-0.16568	0.001632	0.035219	-0.31337	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	VIPR1	vasoactive intestinal polypeptide receptor 1	-0.23496	6.81E-06	0.000909	-0.30575	IM	-0.06642	IM	-0.05639
K64052750	gefitinib	EGFR inhibitor	VSIR	v-type immunoglobulin domain-containing suppressor of t-cell activation	-0.19354	0.000225	0.010113	-0.29158	IM	-0.06642	IM	-0.05639
K67578145	GDC-0879	RAF inhibitor	A2M	alpha-2-macroglobulin	-0.19473	0.00028	0.011644	-0.28495	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	APOD	apolipoprotein d	-0.204	0.000139	0.007331	-0.31016	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.18675	0.000498	0.016875	-0.35895	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.34678	3.72E-11	1.18E-07	-0.3663	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	C3orf70	upf0524 protein c3orf70	-0.21119	7.9E-05	0.005012	-0.31553	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CD96	t-cell surface protein tactile	-0.27983	1.31E-07	5.2E-05	-0.33572	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CDH19	cadherin-19	-0.32149	1.04E-09	1.42E-06	-0.33921	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CHL1	atp-dependent dna helicase ddx11-related	-0.23897	7.42E-06	0.000969	-0.2718	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CMTM5	cklf-like marvel transmembrane domain-containing protein 5	-0.19123	0.000361	0.01374	-0.25048	M	0.110094	M	0.15809

K67578145	GDC-0879	RAF inhibitor	COL19A1	collagen alpha-1	-0.34368	5.68E-11	1.57E-07	-0.37532	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	COL9A3	collagen alpha-3	-0.24562	4.03E-06	0.000623	-0.33425	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.17113	0.001442	0.032684	-0.27829	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CTLA4	cytotoxic t-lymphocyte protein 4	-0.22352	2.87E-05	0.002503	-0.26156	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	CUBN	cubilin	-0.21472	5.95E-05	0.00413	-0.30043	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.24419	4.6E-06	0.000685	-0.33766	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	EDNRB	endothelin receptor type b	-0.31921	1.38E-09	1.77E-06	-0.33396	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FAM180B	protein fam180b	-0.25254	2.09E-06	0.00039	-0.27608	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.23701	8.86E-06	0.001102	-0.31278	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FCGR2B	low affinity immunoglobulin gamma fc region receptor ii-b	-0.28835	5.19E-08	2.6E-05	-0.34392	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FCMR	fas apoptotic inhibitory molecule 3	-0.18429	0.000592	0.01879	-0.25878	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FCRLA	fc receptor-like a	-0.31559	2.16E-09	2.45E-06	-0.393	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.32593	5.9E-10	9.16E-07	-0.32132	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	GAS7	growth arrest-specific protein 7	-0.28738	5.77E-08	2.81E-05	-0.39355	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	GPR55	g-protein coupled receptor 55	-0.24154	5.88E-06	0.000815	-0.31117	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	HPS5	hermansky-pudlak syndrome 5 protein	-0.17848	0.000884	0.024189	-0.25407	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	IL12RB2	interleukin-12 receptor subunit beta-2	-0.25067	2.51E-06	0.000443	-0.2562	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	IL16	pro-interleukin-16	-0.30208	1.09E-08	8.22E-06	-0.44471	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	IRF4	interferon regulatory factor 4	-0.29742	1.87E-08	1.23E-05	-0.40019	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	ITGA9	integrin alpha-9	-0.16361	0.002334	0.043621	-0.29985	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	KCNJ10	atp-sensitive inward rectifier potassium channel 10	-0.24289	5.19E-06	0.000746	-0.27857	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	MIA	melanoma-derived growth regulatory protein	-0.30481	7.9E-09	6.51E-06	-0.40986	M	0.110094	M	0.15809

K67578145	GDC-0879	RAF inhibitor	NFATC2	nuclear factor of activated t-cells; cytoplasmic 2	-0.28788	5.47E-08	2.7E-05	-0.32127	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.17125	0.001431	0.032537	-0.34907	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.27944	1.37E-07	5.34E-05	-0.28505	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	P2RX7	p2x purinoceptor 7	-0.16681	0.001907	0.038637	-0.25968	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PKNOX2	homeobox protein pknox2	-0.2358	9.87E-06	0.001188	-0.31192	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PLEKHO2	pleckstrin homology domain-containing family o member 2	-0.19019	0.00039	0.014408	-0.24616	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PLP1	myelin proteolipid protein	-0.32079	1.13E-09	1.52E-06	-0.38941	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PMP2	myelin p2 protein	-0.34413	5.35E-11	1.51E-07	-0.25593	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.28745	5.73E-08	2.79E-05	-0.35555	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	PTPRZ1	receptor-type tyrosine-protein phosphatase zeta	-0.18312	0.000643	0.019793	-0.34813	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	RENBP	n-acylglucosamine 2-epimerase	-0.21597	5.37E-05	0.003856	-0.28553	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.26738	4.83E-07	0.000135	-0.29934	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SCML4	sex comb on midleg-like protein 4	-0.28099	1.16E-07	4.75E-05	-0.32686	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SHC4	shc-transforming protein 4	-0.25967	1.05E-06	0.000237	-0.27344	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SHROOM4	protein shroom4	-0.19967	0.000193	0.009147	-0.25423	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SLC35F1	solute carrier family 35 member f1	-0.24073	6.32E-06	0.000862	-0.24517	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SORCS1	vps10 domain-containing receptor sorcs1	-0.29938	1.49E-08	1.04E-05	-0.27276	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	SOX5	transcription factor sox-5	-0.20918	9.27E-05	0.005571	-0.29398	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	ST6GALNAC3	alpha-n-acetylgalactosaminide alpha-2;6-sialyltransferase 3	-0.18297	0.00065	0.019928	-0.26558	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	ST8SIA1	alpha-n-acetylneuraminide alpha-2;8-sialyltransferase	-0.25962	1.05E-06	0.000238	-0.26401	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	TAMALIN	protein tamalin	-0.22305	2.98E-05	0.002576	-0.24803	M	0.110094	M	0.15809

K67578145	GDC-0879	RAF inhibitor	TNFRSF14	tumor necrosis factor receptor superfamily member 14	-0.2291	1.78E-05	0.001799	-0.32768	M	0.110094	M	0.15809
K67578145	GDC-0879	RAF inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.26514	6.06E-07	0.00016	-0.31001	M	0.110094	M	0.15809
K69726342	atorvastatin	HMGCR inhibitor	ANGPTL1	angiopoietin-related protein 1	-0.17346	0.000833	0.023275	-0.25955	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	ANTXR1	anthrax toxin receptor 1	-0.17036	0.001034	0.026712	-0.27092	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	ARMCX1	armadillo repeat-containing x-linked protein 1	-0.21491	3.22E-05	0.002713	-0.2517	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	CHST10	carbohydrate sulfotransferase 10	-0.18388	0.000391	0.014446	-0.27109	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.18244	0.000436	0.015485	-0.28967	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	EPHA3	ephrin type-a receptor 3	-0.23994	3.23E-06	0.000533	-0.26891	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	EVC	ellis-van creveld syndrome protein	-0.20553	7.13E-05	0.004684	-0.2736	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	EXTL2	exostosin-2-related	-0.17388	0.000809	0.022863	-0.2948	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	FYN	tyrosine-protein kinase fyn	-0.15868	0.002265	0.042866	-0.26402	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	IFFO1	intermediate filament family orphan 1	-0.19621	0.000152	0.007782	-0.25507	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	LPAR4	lysophosphatidic acid receptor 4	-0.20112	0.000102	0.005959	-0.28366	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	MAP3K3	mitogen-activated protein kinase kinase kinase 3	-0.18539	0.00035	0.01346	-0.24978	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	MOXD1	dbh-like monooxygenase protein 1	-0.20311	8.71E-05	0.005343	-0.2464	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	PDE1C	calcium/calmodulin-dependent 3′,5′-cyclic nucleotide phosphodiesterase 1c	-0.22212	1.71E-05	0.00175	-0.26836	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	RASSF8	ras association domain-containing protein 8	-0.16853	0.001173	0.02884	-0.28561	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.20892	5.37E-05	0.003856	-0.34189	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	SLC35F1	solute carrier family 35 member f1	-0.16358	0.001641	0.035325	-0.26581	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	SPARC	sparc	-0.19929	0.000119	0.006594	-0.25485	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	TIMP2	metalloproteinase inhibitor 2	-0.1812	0.000477	0.016423	-0.23894	M	0.115334	M	0.076984

K69726342	atorvastatin	HMGCR inhibitor	VIM	vimentin	-0.18855	0.000275	0.01153	-0.24243	M	0.115334	M	0.076984
K69726342	atorvastatin	HMGCR inhibitor	ZCCHC24		-0.23137	7.31E-06	0.000958	-0.24867	M	0.115334	M	0.076984
K70914287	BIBX-1382	EGFR inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.18571	0.000341	0.013253	-0.35824	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	COL17A1	collagen alpha-1	-0.29556	7.47E-09	6.23E-06	-0.35198	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.2049	7.51E-05	0.004846	-0.36142	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.30397	2.64E-09	2.85E-06	-0.35553	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.24952	1.25E-06	0.00027	-0.36569	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.20548	7.16E-05	0.004698	-0.32721	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	DSG3	desmoglein-3	-0.32907	9.65E-11	2.36E-07	-0.34731	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.23794	3.92E-06	0.000612	-0.26577	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	ITGB4	integrin beta-4	-0.30844	1.5E-09	1.87E-06	-0.43325	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.29358	9.49E-09	7.45E-06	-0.31999	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.32442	1.82E-10	3.83E-07	-0.27453	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.33811	2.72E-11	9.34E-08	-0.26105	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.30791	1.6E-09	1.95E-06	-0.28773	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.30869	1.45E-09	1.84E-06	-0.39581	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.29938	4.67E-09	4.37E-06	-0.35933	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	S100A8	protein s100-a8	-0.20435	7.86E-05	0.004997	-0.24681	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	SH3BP1	bargin-related	-0.21721	2.64E-05	0.002361	-0.24431	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	SIRPB2	signal-regulatory protein beta-2	-0.24529	1.91E-06	0.000366	-0.25676	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.23944	3.39E-06	0.000553	-0.2628	IM	-0.03277	IM	-0.07259
K70914287	BIBX-1382	EGFR inhibitor	VSIR	v-type immunoglobulin domain-containing	-0.18516	0.000356	0.013612	-0.25087	IM	-0.03277	IM	-0.07259

				suppressor of t-cell activation								
K70914287	BIBX-1382	EGFR inhibitor	ZMYND15	zinc finger mynd domain-containing protein 15	-0.16085	0.001966	0.039377	-0.31983	IM	-0.03277	IM	-0.07259
K72723676	benzethonium	sodium channel blocker	COL19A1	collagen alpha-1	-0.19717	0.000156	0.007922	-0.25833	M	0.156786	M	0.160433
K72723676	benzethonium	sodium channel blocker	COL9A3	collagen alpha-3	-0.1639	0.00173	0.036494	-0.29636	M	0.156786	M	0.160433
K72723676	benzethonium	sodium channel blocker	IL12RB2	interleukin-12 receptor subunit beta-2	-0.25035	1.36E-06	0.000286	-0.26523	M	0.156786	M	0.160433
K72723676	benzethonium	sodium channel blocker	MIA	melanoma-derived growth regulatory protein	-0.17016	0.001136	0.028321	-0.2637	M	0.156786	M	0.160433
K72723676	benzethonium	sodium channel blocker	SGCD	delta-sarcoglycan	-0.16427	0.001687	0.035964	-0.24047	M	0.156786	M	0.160433
K72723676	benzethonium	sodium channel blocker	TMEM229B	transmembrane protein 229b	-0.19379	0.000203	0.009462	-0.23742	M	0.156786	M	0.160433
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	ALOX5	polyunsaturated fatty acid 5-lipoxygenase	-0.22225	1.78E-05	0.001798	-0.27378	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	ANKRD65	ankyrin repeat domain-containing protein 65	-0.17958	0.000557	0.018084	-0.25755	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	CMTM4	cklf-like marvel transmembrane domain-containing protein 4	-0.15962	0.002192	0.042061	-0.29029	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	COL17A1	collagen alpha-1	-0.28881	1.84E-08	1.21E-05	-0.28845	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	CXCL16	c-x-c motif chemokine 16	-0.27048	1.48E-07	5.67E-05	-0.30335	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	DAPP1	dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide	-0.33361	5.79E-11	1.59E-07	-0.36829	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.31007	1.35E-09	1.74E-06	-0.38827	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	DSG3	desmoglein-3	-0.31239	1E-09	1.39E-06	-0.30488	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	FGD3	fyve; rhogef and ph domain-containing protein 3	-0.24179	2.87E-06	0.000489	-0.39	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	HSH2D	hematopoietic sh2 domain-containing protein	-0.24558	1.98E-06	0.000375	-0.2877	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	IL15RA	interleukin-15 receptor subunit alpha	-0.22831	1.03E-05	0.001223	-0.24731	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	ITGB4	integrin beta-4	-0.39573	3.59E-15	1.41E-10	-0.37556	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	KLF8	krueppel-like factor 8	-0.18393	0.000405	0.014761	-0.24754	IM	-0.16658	IM	0.013462

K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	KRT16	keratin; type i cytoskeletal 16	-0.34893	6.43E-12	3.13E-08	-0.3908	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.28716	2.23E-08	1.39E-05	-0.29638	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	KRT5	keratin; type ii cytoskeletal 5	-0.28853	1.9E-08	1.24E-05	-0.3001	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.30003	4.75E-09	4.41E-06	-0.25711	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	LTB	lymphotoxin-beta	-0.20853	5.82E-05	0.00407	-0.24231	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	MAPK10	mitogen-activated protein kinase 10	-0.23304	6.63E-06	0.000892	-0.26455	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	NTN4	netrin-4	-0.23336	6.43E-06	0.000873	-0.25006	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	PSME1	proteasome activator complex subunit 1	-0.16232	0.001837	0.03784	-0.24677	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	PTAFR	platelet-activating factor receptor	-0.31838	4.57E-10	7.54E-07	-0.39812	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	PTPN6	tyrosine-protein phosphatase non-receptor type 6	-0.38357	2.83E-14	7.28E-10	-0.38863	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	SPTLC2	serine palmitoyltransferase 2	-0.16578	0.001458	0.032905	-0.25912	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	TEAD3	transcriptional enhancer factor tef-5	-0.1984	0.000133	0.007116	-0.24584	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	TNFSF10	tumor necrosis factor ligand superfamily member 10	-0.3578	1.71E-12	1.22E-08	-0.2503	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	UNC13D	protein unc-13 homolog d	-0.20426	8.29E-05	0.005171	-0.32715	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	VAV1	proto-oncogene vav	-0.20709	6.56E-05	0.004423	-0.24498	IM	-0.16658	IM	0.013462
K76239644	BMS-690514	EGFR inhibitor; VEGFR inhibitor	VSIR	v-type immunoglobulin domain-containing suppressor of t-cell activation	-0.20258	9.51E-05	0.005674	-0.25307	IM	-0.16658	IM	0.013462
K78096648	oxiperomide	dopamine receptor antagonist	ADAM11	disintegrin and metalloproteinase domain-containing protein 11	-0.19003	0.000293	0.012012	-0.26832	M	0.16608	MSL/M	0.085408
K78096648	oxiperomide	dopamine receptor antagonist	DVL2	segment polarity protein dishevelled homolog dvl-2	-0.17028	0.0012	0.029232	-0.25866	M	0.16608	MSL/M	0.085408
K78096648	oxiperomide	dopamine receptor antagonist	KBTBD6	kelch repeat and btb domain-containing protein 6	-0.16844	0.001359	0.031527	-0.23969	M	0.16608	MSL/M	0.085408
K78096648	oxiperomide	dopamine receptor antagonist	KCNJ4	inward rectifier potassium channel 4	-0.15711	0.002836	0.048942	-0.25506	M	0.16608	MSL/M	0.085408

K78096648	oxiperomide	dopamine receptor antagonist	MLLT1	protein enl	-0.16583	0.001616	0.035009	-0.32063	M	0.16608	MSL/M	0.085408
K78096648	oxiperomide	dopamine receptor antagonist	ZNF101	zinc finger protein 101	-0.15976	0.002397	0.044342	-0.26227	M	0.16608	MSL/M	0.085408
K80343549	TAK-285	EGFR inhibitor	DENND1C	denn domain-containing protein 1c	-0.16238	0.002243	0.042614	-0.26121	IM	-0.07158	IM	-0.06872
K80343549	TAK-285	EGFR inhibitor	DENND2D	denn domain-containing protein 2d	-0.16242	0.002238	0.042562	-0.27192	IM	-0.07158	IM	-0.06872
K80343549	TAK-285	EGFR inhibitor	ITGB4	integrin beta-4	-0.17623	0.000898	0.024425	-0.3462	IM	-0.07158	IM	-0.06872
K80343549	TAK-285	EGFR inhibitor	LPAR5	lysophosphatidic acid receptor 5	-0.22432	2.16E-05	0.002054	-0.27437	IM	-0.07158	IM	-0.06872
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	ADAM23	disintegrin and metalloproteinase domain-containing protein 23	-0.19822	0.000129	0.006981	-0.2473	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	AEBP1	adipocyte enhancer-binding protein 1	-0.16893	0.001142	0.028405	-0.24081	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	ARHGAP31	rho gtpase-activating protein 31	-0.21747	2.58E-05	0.002321	-0.24902	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	ARMCX1	armadillo repeat-containing x-linked protein 1	-0.20299	8.79E-05	0.005378	-0.26747	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	ATP8B2	phospholipid-transporting atpase id	-0.18501	0.00036	0.013711	-0.28343	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	CCDC136	coiled-coil domain-containing protein 136	-0.18589	0.000337	0.013135	-0.25096	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	CHST10	carbohydrate sulfotransferase 10	-0.16637	0.00136	0.031538	-0.30247	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	CNRIP1	cb1 cannabinoid receptor-interacting protein 1	-0.17278	0.000874	0.024004	-0.25165	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	COL19A1	collagen alpha-1	-0.19598	0.000155	0.00787	-0.25227	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	CYP2U1	cytochrome p450 2u1	-0.21352	3.63E-05	0.002948	-0.29102	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	EPHA3	ephrin type-a receptor 3	-0.16609	0.001386	0.031919	-0.28147	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	FAM180B	protein fam180b	-0.16123	0.001918	0.03878	-0.24692	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	FGD1	fyve; rhogef and ph domain-containing protein 1	-0.18426	0.000381	0.014197	-0.25211	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	GPR161	g-protein coupled receptor 161	-0.1866	0.000319	0.012686	-0.24182	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	HMCN1	hemicentin-1	-0.18187	0.000454	0.015911	-0.25492	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	IL16	pro-interleukin-16	-0.21421	3.42E-05	0.002828	-0.28116	M	0.101093	M	0.191571

K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	IRF4	interferon regulatory factor 4	-0.15807	0.002357	0.043888	-0.24649	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	LIX1L	lix1-like protein	-0.21023	4.81E-05	0.003575	-0.2552	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	MCOLN2	mucolipin-2	-0.20922	5.24E-05	0.003792	-0.27402	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.21782	2.5E-05	0.002273	-0.27097	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	PRKD1		-0.20553	7.13E-05	0.004684	-0.29262	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	PYGO1	pygopus homolog 1	-0.20407	8.05E-05	0.005071	-0.27335	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	RHOJ	rho-related gtp-binding protein rhoj	-0.21861	2.33E-05	0.002164	-0.2411	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	RUNX3	runt-related transcription factor 3	-0.16417	0.001577	0.034497	-0.24933	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	SGCD	delta-sarcoglycan	-0.17142	0.000961	0.025493	-0.24557	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	SMO	smoothened homolog	-0.19623	0.000152	0.007777	-0.307	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	SPART	spartin	-0.1863	0.000327	0.012888	-0.25979	M	0.101093	M	0.191571
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	WIPF1	was/wasl-interacting protein family member 1	-0.19352	0.000188	0.008961	-0.24425	M	0.101093	M	0.191571
K94455792	ICG-001	beta-catenin inhibitor	CSPG4	chondroitin sulfate proteoglycan 4	-0.19632	0.000157	0.007939	-0.23968	M	0.178329	M	0.163484
K94455792	ICG-001	beta-catenin inhibitor	MYH10	myosin-10	-0.1641	0.001632	0.035219	-0.27195	M	0.178329	M	0.163484
K94455792	ICG-001	beta-catenin inhibitor	RCN2	reticulocalbin-2	-0.18914	0.000274	0.011481	-0.2527	M	0.178329	M	0.163484
K94455792	ICG-001	beta-catenin inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.17678	0.000681	0.020514	-0.26506	M	0.178329	M	0.163484
K08542803	gambogic-acid	caspase activator	FRMD6	ferm domain-containing protein 6	-0.19335	0.00021	0.030901	-0.31589	M	-0.03027	M	-0.00196
K09951645	dabrafenib	RAF inhibitor	ASB2	ankyrin repeat and socs box protein 2	-0.25863	8.69E-07	0.001428	-0.39736	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.29464	1.76E-08	0.000133	-0.41865	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	CDH19	cadherin-19	-0.21686	4.08E-05	0.012828	-0.31348	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	CHST11	carbohydrate sulfotransferase 11	-0.19116	0.00031	0.03747	-0.30972	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	COL19A1	collagen alpha-1	-0.29259	2.23E-08	0.000153	-0.40195	M	0.043133	M	0.14386

K09951645	dabrafenib	RAF inhibitor	DAAM2	disheveled-associated activator of morphogenesis 2	-0.2037	0.000119	0.023095	-0.30795	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	EDNRB	endothelin receptor type b	-0.2923	2.31E-08	0.000154	-0.36828	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	FCGR2A	low affinity immunoglobulin gamma fc region receptor ii-a-related	-0.2823	7.14E-08	0.000321	-0.30776	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	FCRLA	fc receptor-like a	-0.32782	2.91E-10	1E-05	-0.39273	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	GAS7	growth arrest-specific protein 7	-0.22244	2.54E-05	0.009936	-0.37622	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	GYPC	glycophorin-c	-0.30953	2.98E-09	4.47E-05	-0.30487	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	HPS5	hermansky-pudlak syndrome 5 protein	-0.21148	6.36E-05	0.016397	-0.30601	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	IL16	pro-interleukin-16	-0.26016	7.46E-07	0.001299	-0.39859	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	IRF4	interferon regulatory factor 4	-0.27643	1.36E-07	0.000479	-0.33551	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	ITGB3	integrin beta-3	-0.22968	1.35E-05	0.006964	-0.35606	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	LPXN	leupaxin	-0.2402	5.18E-06	0.004057	-0.31391	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	MIA	melanoma-derived growth regulatory protein	-0.26532	4.4E-07	0.000942	-0.37161	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	NFATC2	nuclear factor of activated t-cells; cytoplasmic 2	-0.26331	5.41E-07	0.001055	-0.32185	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	PLP1	myelin proteolipid protein	-0.30462	5.41E-09	6.64E-05	-0.35707	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	PTCRA	pre t-cell antigen receptor alpha	-0.30249	6.99E-09	7.87E-05	-0.41346	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	SHROOM4	protein shroom4	-0.34578	2.54E-11	2.08E-06	-0.34358	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	SRPX	sushi repeat-containing protein srpx	-0.23172	1.12E-05	0.006318	-0.3477	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	STK10	serine/threonine-protein kinase 10	-0.20043	0.000153	0.02638	-0.33469	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	TRPV2	transient receptor potential cation channel subfamily v member 2	-0.30149	7.87E-09	8.51E-05	-0.35302	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	WWTR1	ww domain-containing transcription regulator protein 1	-0.24661	2.83E-06	0.002923	-0.34605	M	0.043133	M	0.14386
K13169950	NSC-3852	HDAC inhibitor	MPP2	forkhead box protein m1	-0.19379	0.000212	0.031005	-0.29806	M	0.093556	M	-0.00012

K25970317	resibufogenin	Na/K-ATPase inhibitor	B4GALNT1	beta-1,4 n-acetylgalactosaminyltransferase 1	-0.25891	9.09E-07	0.001476	-0.31383	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	BEND6	ben domain-containing protein 6	-0.20376	0.000124	0.023598	-0.33503	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	DCLK2	serine/threonine-protein kinase dclk2	-0.25035	2.11E-06	0.002505	-0.29911	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	FERMT2	fermitin family homolog 2	-0.27164	2.46E-07	0.000679	-0.34523	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	FHL1	four and a half lim domains protein 1	-0.22738	1.75E-05	0.00807	-0.39527	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	LRRC8C	volume-regulated anion channel subunit lrrc8c	-0.21149	6.67E-05	0.016817	-0.29933	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	MRC2	c-type mannose receptor 2	-0.25267	1.68E-06	0.002166	-0.33962	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	MSRB3	methionine-r-sulfoxide reductase b3	-0.26092	7.42E-07	0.001299	-0.38269	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.29869	1.21E-08	0.000107	-0.30644	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	TLCD5	tlc domain-containing protein 5	-0.23238	1.12E-05	0.006318	-0.37712	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	TRPC1	short transient receptor potential channel 1	-0.27139	2.52E-07	0.000695	-0.33298	MSL	-0.05263	MSL	-0.09203
K25970317	resibufogenin	Na/K-ATPase inhibitor	ZEB1	zinc finger e-box-binding homeobox 1	-0.26988	2.95E-07	0.000761	-0.31193	MSL	-0.05263	MSL	-0.09203
K61443650	thiomersal	other antibiotic	FMNL3	formin-like protein 3	-0.23623	4.62E-06	0.003823	-0.3199	M	-0.05708	M	0.028697
K61443650	thiomersal	other antibiotic	PIK3CD	phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	-0.23165	7.12E-06	0.004948	-0.31557	M	-0.05708	M	0.028697
K61443650	thiomersal	other antibiotic	PRTG	protogenin	-0.22174	1.76E-05	0.008119	-0.30441	M	-0.05708	M	0.028697
K84868168	erdafitinib	FGFR inhibitor	ATP8B2	phospholipid-transporting atpase id	-0.19857	0.000185	0.029047	-0.30762	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	CNTNAP1	contactin-associated protein 1	-0.25595	1.22E-06	0.00177	-0.3174	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	DCLK2	serine/threonine-protein kinase dclk2	-0.23933	5.97E-06	0.004446	-0.31828	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	FBN1	fibrillin-1	-0.2825	7.62E-08	0.000328	-0.30056	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	FGFR1	fibroblast growth factor receptor 1	-0.31842	1.09E-09	2.55E-05	-0.35083	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	FHL1	four and a half lim domains protein 1	-0.19794	0.000194	0.029783	-0.30652	MSL	-0.0744	MSL/M	0.006092

K84868168	erdafitinib	FGFR inhibitor	GLI1	zinc finger protein gli1	-0.20185	0.000144	0.025558	-0.33185	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	GLIPR2	golgi-associated plant pathogenesis-related protein 1	-0.31212	2.4E-09	4.11E-05	-0.31536	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	MAP1B	microtubule-associated protein 1b	-0.24434	3.74E-06	0.003398	-0.32118	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	MEX3B	rna-binding protein mex3b	-0.19734	0.000203	0.030421	-0.31704	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	MRAS	ras-related protein m-ras	-0.26462	5.1E-07	0.001031	-0.30048	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	MRC2	c-type mannose receptor 2	-0.20138	0.000149	0.025983	-0.36328	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	MSRB3	methionine-r-sulfoxide reductase b3	-0.29951	1.1E-08	0.000104	-0.31656	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	NLGN2	neuroligin-2	-0.2421	4.62E-06	0.003823	-0.3305	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	NREP	neuronal regeneration-related protein	-0.19768	0.000198	0.030069	-0.32394	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	PDGFRB	platelet-derived growth factor receptor beta	-0.33939	6.98E-11	3.82E-06	-0.3048	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	RBPMS2	rna-binding protein with multiple splicing 2	-0.19068	0.000334	0.038903	-0.3019	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	SYDE1	rho gtpase-activating protein syde1	-0.27347	2.02E-07	0.000615	-0.29962	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	TTC28	tetratricopeptide repeat protein 28	-0.2646	5.11E-07	0.001031	-0.31995	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	TUBA1A	tubulin alpha-1a chain	-0.22155	2.89E-05	0.010639	-0.3389	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	VASH1	tubulinyl-tyr carboxypeptidase 1	-0.19412	0.000259	0.034218	-0.33053	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	VIM	vimentin	-0.26067	7.61E-07	0.001311	-0.32641	MSL	-0.0744	MSL/M	0.006092
K84868168	erdafitinib	FGFR inhibitor	ZEB1	zinc finger e-box-binding homeobox 1	-0.27392	1.93E-07	0.000598	-0.31151	MSL	-0.0744	MSL/M	0.006092
K94441233	mevastatin	HMGCR inhibitor	CAVIN1	caveolae-associated protein 1	-0.27085	3.38E-07	0.000819	-0.33251	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	CCDC80	coiled-coil domain-containing protein 80	-0.21025	8.52E-05	0.01925	-0.31342	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	COL13A1	collagen alpha-1	-0.20335	0.000146	0.02572	-0.34946	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	EVC	ellis-van creveld syndrome protein	-0.30251	1.03E-08	0.000104	-0.3209	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	HEG1	protein heg homolog 1	-0.2727	2.79E-07	0.000738	-0.36346	MSL	-0.00119	MSL	-0.09323

K94441233	mevastatin	HMGCR inhibitor	LAYN	layilin	-0.23458	1.1E-05	0.006258	-0.31407	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	MAP3K3	mitogen-activated protein kinase kinase kinase 3	-0.20686	0.000111	0.022463	-0.30851	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	MCAM	cell surface glycoprotein muc18	-0.22153	3.39E-05	0.01158	-0.31283	MSL	-0.00119	MSL	-0.09323
K94441233	mevastatin	HMGCR inhibitor	PIK3CD	phosphatidylinositol 4;5-bisphosphate 3-kinase catalytic subunit delta isoform	-0.21451	6.05E-05	0.016012	-0.30633	MSL	-0.00119	MSL	-0.09323

[0322] Table 24B: Mechanism of action and associated subtype for selected compounds with significant subtype association.

BROAD compound ID	Compound Name	MoA	Associated Gene	Associated Gene Family	compound gene train corr	compound gene train pvalue	compound gene test corr	compound gene dep train corr	compound gene dep train pvalue	compound gene dep test corr	TNBCType train	DTIO Corr train	TNBCType test	DTIO Corr test
K09951645	dabrafenib	RAF inhibitor	SH2D1B	sh2 domain-containing protein 1b	-0.11236	0.035098	-0.25099	-0.20891	0.000699	-0.24599	M	0.043133	M	0.14386
K09951645	dabrafenib	RAF inhibitor	EVC2	limbin	-0.12568	0.018328	-0.15596	-0.14925	0.040389	-0.24637	M	0.043133	M	0.14386
K20285085	R406	SYK inhibitor	CRMP1	dihydropyrimidinase-related protein 1	-0.1488	0.005151	-0.15157	-0.15198	0.036823	-0.26917	MSL	-0.1076	MSL	-0.04153
K72327355	baicalein	lipoxygenase inhibitor	PRICKLE2	prickle-like protein 2	-0.15967	0.002312	-0.22131	-0.20953	0.021081	-0.23851	IM	-0.14417	IM	-0.04244
K39974922	lenvatinib	FGFR inhibitor; KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	DCLK2	serine/threonine-protein kinase dclk2	-0.20098	0.000132	-0.26734	-0.13985	0.022271	-0.17941	MSL	-0.03256	M	0.002695
K84868168	erdafitinib	FGFR inhibitor	EBF1	transcription factor coe1	-0.10611	0.047295	-0.1734	-0.13163	0.03252	-0.1897	MSL	-0.0744	M	0.006092
A00842753	oleuropein	estrogen receptor agonist	FBN1	fibrillin-1	-0.11021	0.039319	-0.19084	-0.16182	0.024937	-0.19376	MSL	-0.00213	MSL	0.021715
K20285085	R406	SYK inhibitor	FHL1	four and a half lim domains protein 1	-0.25729	9.95E-07	-0.19191	-0.21511	0.019323	-0.26019	MSL	-0.1076	MSL	-0.04153
K39974922	lenvatinib	FGFR inhibitor; KIT inhibitor; PDGFR tyrosine kinase	NFASC	neurofascin	-0.15569	0.003184	-0.16642	-0.13017	0.044397	-0.18236	MSL	-0.03256	M	0.002695

		receptor inhibitor; VEGFR inhibitor											
K94441233	mevastatin	HMGCR inhibitor	ABL1	tyrosine-protein kinase abl1	-0.12545	0.01994	-0.14942	-0.14081	0.023967	-0.2168	MSL	-0.00119	MSL	-0.09323
K75958547	pitavastatin	HMGCR inhibitor	IL4I1	l-amino-acid oxidase	-0.10707	0.040092	-0.25368	-0.22129	0.001778	-0.21053	MSL	-0.04476	M	-0.0837
K17203476	LY2874455	FGFR antagonist	CAVIN1	caveolae-associated protein 1	-0.19016	0.000244	-0.20469	-0.18906	0.007798	-0.24234	IM	-0.14489	MSL	-0.0838
K09951645	dabrafenib	RAF inhibitor	LCP2	lymphocyte cytosolic protein 2	-0.15397	0.003783	-0.17003	-0.25728	2.77E-05	-0.30414	M	0.043133	M	0.14386
K75958547	pitavastatin	HMGCR inhibitor	LTBP2		-0.16591	0.001403	-0.25061	-0.1581	0.026493	-0.22687	MSL	-0.04476	M	-0.0837
K08542803	gambogic-acid	caspase activator	MICB	mhc class i polypeptide-related sequence a-related	-0.16383	0.001738	-0.205	-0.12811	0.035033	-0.17798	M	-0.03027	M	-0.00196
K02113016	olaparib	PARP inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.22693	1.3E-05	-0.2403	-0.12235	0.044173	-0.21218	M	0.026605	M	0.064041
K13044802	ciclopirox	membrane integrity inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.12618	0.015437	-0.17936	-0.14154	0.018859	-0.26998	IM	-0.15742	IM	-0.06749
K13169950	NSC-3852	HDAC inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.12525	0.017274	-0.20879	-0.12204	0.045123	-0.24502	M	0.093556	M	-0.00012
K54955827	niraparib	PARP inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.12615	0.017891	-0.2096	-0.13507	0.027622	-0.21753	M	0.035768	M	-0.03477
K75958547	pitavastatin	HMGCR inhibitor	PTPN14	tyrosine-protein phosphatase non-receptor type 14	-0.22104	1.88E-05	-0.28287	-0.12737	0.034757	-0.16688	MSL	-0.04476	M	-0.0837
K03289018	CCT137690	Aurora kinase inhibitor	PTPRG	receptor-type tyrosine-protein phosphatase gamma	-0.16073	0.00201	-0.19761	-0.1761	0.003449	-0.16896	M	-0.02552	M	-0.13958
K54955827	niraparib	PARP inhibitor	FAT4	protocadherin fat 4	-0.11104	0.037319	-0.16653	-0.23812	0.000827	-0.19313	M	0.035768	M	-0.03477
K61688984	RGFP966	HDAC inhibitor	LIMD2		-0.17338	0.000866	-0.21277	-0.19938	0.027689	-0.26501	MSL	0.069122	IM	-0.02541
K75958547	pitavastatin	HMGCR inhibitor	RASSF4	ras and rab interactor 2	-0.13101	0.011889	-0.25647	-0.20299	0.024936	-0.40468	MSL	-0.04476	M	-0.0837
K84868168	erdafitinib	FGFR inhibitor	CACNA1G	voltage-dependent t-type calcium	-0.11953	0.025334	-0.17592	-0.14067	0.022248	-0.18424	MSL	-0.0744	M	0.006092

K13169950	NSC-3852	HDAC inhibitor	ADAMTSL1	neuronal regeneration-related protein	-0.15882	0.002476	-0.18811	-0.2034	0.025243	-0.26133	M	0.093556	M	-0.00012
K84868168	erdafitinib	FGFR inhibitor	NREP		-0.19768	0.000198	-0.32394	-0.31993	0.000368	-0.43505	MSL	-0.0744	M	0.006092
A19736161	ondansetron	serotonin receptor antagonist	EPSTI1	epithelial-stromal interaction protein 1	-0.14488	0.005359	-0.1616	-0.15834	0.012533	-0.19919	IM	-0.07634	IM	-0.11235
K79821389	rubitecan	topoisomerase inhibitor	EBI3	interleukin-27 subunit beta	-0.11499	0.031497	-0.18602	-0.25324	3.25E-05	-0.20379	IM	-0.11776	IM	-0.06417
K67578145	GDC-0879	RAF inhibitor	TNFSF13B	tumor necrosis factor ligand superfamily member 13b	-0.11464	0.03354	-0.15832	-0.19925	0.006548	-0.20293	M	0.110094	M	0.15809
K19333160	RKI-1447	rho associated kinase inhibitor	FBXO17	f-box only protein 17	-0.18772	0.000305	-0.19525	-0.15882	0.008569	-0.21333	MSL	0.046328	MSL	0.081223
K67578145	GDC-0879	RAF inhibitor	SH2D1B	sh2 domain-containing protein 1b	-0.13502	0.012187	-0.20015	-0.14902	0.016814	-0.20635	M	0.110094	M	0.15809
K94455792	ICG-001	beta-catenin inhibitor	EDNRB	endothelin receptor type b	-0.18843	0.000289	-0.15061	-0.16395	0.006632	-0.23104	M	0.178329	M	0.163484
K19687926	lapatinib	EGFR inhibitor	EPHB3	ephrin type-b receptor 3	-0.14608	0.005046	-0.18741	-0.15157	0.012005	-0.16446	IM	-0.08369	IM	-0.0302
K42805893	osimertinib	EGFR inhibitor	EPHB3	ephrin type-b receptor 3	-0.14965	0.004011	-0.29476	-0.18764	0.001776	-0.17527	IM	-0.06781	IM	0.075302
K46386702	ARRY-334543	EGFR inhibitor	EPHB3	ephrin type-b receptor 3	-0.14245	0.006482	-0.2314	-0.14635	0.015515	-0.21657	IM	-0.05992	IM	-0.03109
K05804044	AZ-628	RAF inhibitor	FLT1	vascular endothelial growth factor receptor 1	-0.30989	1.53E-09	-0.26232	-0.15815	0.008857	-0.1733	M	0.190801	M	0.324717
K13394247	radafaxine	dopamine norepinephrine reuptake inhibitor	SYNM	asparagine--tRNA ligase, mitochondrial-related	-0.11637	0.029509	-0.17284	-0.15372	0.033271	-0.2128	M	0.059801	MSL	-0.04236
K12040459	AT7867	AKT inhibitor	RCOR2	rest corepressor 2	-0.16454	0.001633	-0.21449	-0.14352	0.024367	-0.17868	MSL	0.048117	M	0.003574
A12230535	nutlin-3	MDM inhibitor	HSPG2	basement membrane-specific heparan sulfate proteoglycan core protein	-0.12664	0.017451	-0.21153	-0.18337	0.01155	-0.24656	M	0.160633	M	0.150256

K81332461	maxacalcitol	vitamin D receptor agonist	ITGB4	integrin beta-4	-0.13978	0.008639	-0.35213	-0.12972	0.036948	-0.17447	IM	-0.07504	IM	-0.00506
K31866293	TAK-632	RAF inhibitor	NRROS	transforming growth factor beta activator lrrc33	-0.24743	1.65E-06	-0.29319	-0.12524	0.048374	-0.20673	M	0.084888	M	0.20887
K56981171	brigatinib	ALK tyrosine kinase receptor inhibitor; EGFR inhibitor	KRT17	keratin; type i cytoskeletal 17	-0.26518	4.81E-07	-0.18505	-0.20637	0.004081	-0.18953	IM	-0.17279	IM	0.040238
A56085258	LGX818	RAF inhibitor	LCP2	lymphocyte cytosolic protein 2	-0.19511	0.000166	-0.23289	-0.20467	0.000653	-0.23575	M	0.095349	M	0.14417
K26818574	BIX-01294	histone lysine methyltransferase inhibitor	NGFR	tumor necrosis factor receptor superfamily member 16	-0.15854	0.002351	-0.26243	-0.20577	0.000624	-0.17753	M	0.083765	M	0.246345
K12040459	AT7867	AKT inhibitor	CLEC1A	c-type lectin domain family 1 member a	-0.13105	0.012334	-0.18863	-0.12532	0.038525	-0.2028	MSL	0.048117	M	0.003574
A56085258	LGX818	RAF inhibitor	PLXNB3	plexin-b3	-0.18322	0.000411	-0.27828	-0.16993	0.004793	-0.2418	M	0.095349	M	0.14417
K05804044	AZ-628	RAF inhibitor	PLXNB3	plexin-b3	-0.22015	2.26E-05	-0.26462	-0.14752	0.014886	-0.19098	M	0.190801	M	0.324717
K31866293	TAK-632	RAF inhibitor	PLXNB3	plexin-b3	-0.11197	0.032232	-0.24065	-0.14213	0.019017	-0.26994	M	0.084888	M	0.20887
K13183738	pentamidine	anti-pneumocystis agent	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.15586	0.002867	-0.3033	-0.20342	0.000722	-0.23393	M	0.215745	M	0.139961
K29905972	axitinib	PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.13705	0.00913	-0.21957	-0.18554	0.002205	-0.24346	M	0.081599	M	0.004812
K47150025	KI-8751	KIT inhibitor; PDGFR tyrosine kinase receptor inhibitor; VEGFR inhibitor	POLR2A	dna-directed rna polymerase ii subunit rpb1	-0.11823	0.023693	-0.27588	-0.15532	0.010168	-0.23856	M	0.025124	M	0.037321
K77791657	3-deazaneplanocin-A	histone lysine methyltransferase inhibitor	PSMA3	proteasome subunit alpha type-3	-0.18919	0.000267	-0.16247	-0.20043	0.00083	-0.35165	IM	-0.1309	IM	-0.05245
K16180792	bis(maltolato)oxovanadium(IV)	tyrosine phosphatase inhibitor	PTPN14	tyrosine-protein phosphatase non-receptor type 14	-0.10809	0.042695	-0.22066	-0.18412	0.002573	-0.27993	M	0.148517	M	0.090307
K31866293	TAK-632	RAF inhibitor	BCL2A1	bcl-2-related protein a1	-0.23617	4.93E-06	-0.26144	-0.16506	0.020778	-0.26705	M	0.084888	M	0.20887
K19687926	lapatinib	EGFR inhibitor	TMPRSS3	transmembrane protease serine 4	-0.12707	0.014857	-0.21639	-0.13638	0.023963	-0.1645	IM	-0.08369	IM	-0.0302

K37561857	zardaverine	phosphodiesterase inhibitor	TACC1	transforming acidic coiled-coil-containing protein 1	-0.13693	0.009586	-0.16647	-0.18834	0.039393	-0.31546	M	0.178243	MSL	0.169947
K93123848	RAF265	RAF inhibitor; VEGFR inhibitor	CNTNAP1	contactin-associated protein 1	-0.19589	0.000156	-0.17363	-0.25722	0.000263	-0.26581	M	0.101093	M	0.191571
A75975749	bafetinib	Bcr-Abl kinase inhibitor; LYN tyrosine kinase inhibitor	LPXN	leupaxin	-0.2009	0.000155	-0.27465	-0.18253	0.011277	-0.26801	M	0.119134	M	0.165805
K94455792	ICG-001	beta-catenin inhibitor	SH3PXD2A	sh3 and px domain-containing protein 2a	-0.13274	0.011019	-0.19148	-0.2288	0.011249	-0.27796	M	0.178329	M	0.163484

[0323] Table 24A and 24B key

MoA: Mechanism of action.

Associated Gene: Gene whose expression correlated with compound sensitivity across cell lines.

Associated Gene Family: Protein family in which that gene is found.

compound gene train corr: Correlation of gene expression with compound sensitivity in the training data. Strong negative correlation means that greater expression was linked to increased sensitivity to the compounds.

compound gene train pvalue: Measure of significance for this association.

compound gene test corr: Correlation in the test data.

compound gene dep train corr: Correlation of gene dependency with compound sensitivity in the training data set. A negative correlation means that the importance of the expression of that gene to cell health was linked to increased compound sensitivity.

compound gene dep train pvalue: Measure of significance for this association.

compound gene dep test corr: Correlation of gene dependency with compound sensitivity in the test data set.

TNBCType train: Classification of association of the compound sensitivity with the IM, MSL and M cell line classes in the training data set.

DTIO Corr train: Association of the compound sensitivity with the DetermaIO cell line classes in the training data set.

TNBCType test: Classification of the association of the compound sensitivity with the IM, MSL and M cell line classes in the test data set.

DTIO Corr test: Association of the compound sensitivity with the DetermaIO cell line classes in the test data set.

[0324] Table 25: Unique compounds identified through assessment of compound:gene and compound:gene:gene dependency correlations.

BROAD compound ID	Compound Name	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations
A00842753	RGFP966		X
A12230535	TAK-285		X
A19736161	benzethonium		X
A19777893	oleuropein	X	
A27883417	nutlin-3	X	
A56085258	ondansetron	X	X

A75975749	menadione-bisulfite	X	X
K01507359	alexidine	X	
K02113016	gefitinib		X
K03289018	BIBX-1382		X
K03765900	LGX818	X	
K04568635	bafetinib	X	
K05804044	rifampin	X	X
K07106112	olaparib	X	
K08542803	dasatinib	X	X
K09416995	CCT137690	X	
K09951645	chlorhexidine	X	X
K12040459	rubitecan		X
K13044802	GDC-0879		X
K13060017	XL-647	X	
K13169950	PR-619	X	X
K13183738	octenidine	X	X
K13394247	oxiperomide		X
K16180792	AZ-628	X	X
K17203476	dihydroartemisinin		X
K19333160	BMS-599626	X	X
K19540840	gambogic-acid	X	
K19687926	BMS-690514		X
K20285085	UNC0642		X
K22134346	lovastatin	X	
K23190681	dabrafenib	X	
K23925186	AT7867	X	
K25970317	artesunate	X	
K26603252	ciclopirox	X	
K26818574	UNC0631	X	X
K28061410	NSC-3852	X	
K28824103	pentamidine	X	
K29905972	RAF265		X
K30159788	radafaxine	X	
K30933884	bis(maltolato)oxovanadium(IV)	X	
K31698212	LY2874455	X	
K31866293	RKI-1447	X	X
K33882852	saracatinib	X	
K37561857	lapatinib	X	X
K39974922	thiomersal		X
K40109029	R406	X	
K42805893	3-deazaneplanocin-A		X
K46386702	simvastatin	X	X
K47150025	mevastatin		X

K49294207	AV-412	X	
K49328571	oridonin	X	
K52256627	resibufogenin	X	
K54395039	PD-153035	X	
K54634444	BIX-01294	X	
K54955827	atorvastatin		X
K56981171	erdafitinib		X
K58529924	beta-lapachone	X	
K60130390	genipin	X	
K60443845	axitinib	X	
K61443650	niraparib	X	
K61688984	baicalein		X
K62200014	RSV604	X	
K62213621	UNBS-5162	X	
K64052750	icotinib	X	
K67578145	TAK-632	X	X
K69726342	ZK-93423	X	
K70914287	zardaverine	X	
K72327355	chlormidazole		X
K72723676	lenvatinib	X	
K75958547	anagrelide		X
K76239644	SB-505124	X	
K77791657	ICG-001		X
K78096648	osimertinib	X	
K79821389	pitavastatin		X
K80343549	ARRY-334543	X	
K81332461	maxacalcitol		X
K84868168	selumetinib	X	X
K93123848	KI-8751	X	X
K94441233	ONC201	X	X
K94455792	BIBU-1361	X	X

[0325] Table 26: Unique genes identified through assessment of compound:gene and compound:gene:gene dependency correlations.

Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations	Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations	Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations	Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations	Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations	Gene	Present in compound:gene correlations	Present in compound:gene:gene dependency correlations
A2M	X		CMTM4	X		FGL2	X		KRT16	X		PDGFRB	X		SHROOM4	X	
ABCA8	X		CMTM5	X		FHL1	X	X	KRT17	X	X	PDZD4	X		SIRPB2	X	
ABI2	X		CNRIP1	X		FKBP7	X		KRT5	X		PDZRN3	X		SLC35F1	X	
ABL1		X	CNTNAP1	X	X	FLT1	X	X	LAMA4	X		PEAK1	X		SLC6A12	X	
ACACB	X		COL13A1	X		FMNL3	X		LARP6	X		PHC1	X		SMIM10	X	
ACTR3B	X		COL17A1	X		FN1	X		LAYN	X		PHYHIP	X		SMO	X	
ADAM11	X		COL19A1	X		FOXO3B	X		LCP2	X	X	PIANP	X		SNX10	X	
ADAM23	X		COL4A2	X		FRMD6	X		LGALS9	X		PIK3CD	X		SORBS1	X	
ADAM8	X		COL9A3	X		FYN	X		LIMD2		X	PIP4K2B	X		SORCS1	X	
ADAMTS1	X		COROO2B	X		GALNT17	X		LIX1L	X		PKNOX2	X		SORCS2	X	
ADAMTS9	X		CPQ	X		GAS7	X		LPAR4	X		PLAAT4	X		SOX5	X	
ADAMTSL1		X	CRMP1		X	GASK1B	X		LPAR5	X		PLEKHO1	X		SPARC	X	
ADGRB2	X		CSPG4	X		GDNF	X		LPXN	X	X	PLEKHO2	X		SPART	X	
AEBP1	X		CST7	X		GHR	X		LRRC8C	X		PLP1	X		SPTLC2	X	
ALOX5	X		CTLA4	X		GLI1	X		LSAMP	X		PLPP7	X		SRGN	X	

AMOTL1	X		CUBN	X		GLIPR2	X		LTB	X		PLXNB3	X	X	SRPX	X	
ANGPTL1	X		CXCL16	X		GNG2	X		LTBP2		X	PLXNC1	X		ST3GAL2	X	
ANGPTL7	X		CYBRD1	X		GNG7	X		LUM	X		PMP2	X		ST3GAL5	X	
ANKRD33B	X		CYGB	X		GPC3	X		LYL1	X		POLR2A	X	X	ST6GALNAC3	X	
ANKRD44	X		CYP2U1	X		GPC6	X		LZTS1	X		PRICKLE2		X	ST8SIA1	X	
ANKRD65	X		CYP4B1	X		GPR161	X		LZTS2	X		PRKD1	X		STARD9	X	
ANTXR1	X		DAAM2	X		GPR162	X		MAP1B	X		PRTG	X		STK10	X	
ANXA6	X		DACT3	X		GPR55	X		MAP3K3	X		PSMA3		X	STK32B	X	
APOD	X		DAPP1	X		GPSM1	X		MAPK10	X		PSME1	X		SYDE1	X	
APOL1	X		DCLK2	X	X	GPSM3	X		MCAM	X		PTAFR	X		SYNM	X	X
APOLD1	X		DENND1C	X		GSN	X		MCC	X		PTCRA	X		SYPL2	X	
ARHGAP30	X		DENND2D	X		GUCY1A2	X		MCOLN2	X		PTK7	X		SYTL3	X	
ARHGAP31	X		DIRAS1	X		GYPC	X		MEF2C	X		PTN	X		TACC1		X
ARHGDIB	X		DKK2	X		HAND2	X		MEX3A	X		PTPN14		X	TAMALIN	X	
ARHGEF4	X		DLC1	X		HEG1	X		MEX3B	X		PTPN14		X	TEAD3	X	
ARL10	X		DLG4	X		HGF	X		MFGE8	X		PTPN6	X		TIMP2	X	
ARMCX1	X		DLX2	X		HMCN1	X		MFNG	X		PTPRG		X	TIMP3	X	
ASB2	X		DLX5	X		HPS5	X		MIA	X		PTPRM	X		TLCD5	X	
ATOH8	X		DLX6	X		HSH2D	X		MICB		X	PTPRZ1	X		TMEM229B	X	
ATP8B2	X		DRAM1	X		HSPG2		X	MICU3	X		PYGO1	X		TMEM255A	X	

B4GALNT1	X		DSG3	X		HTRA1	X		MLLT1	X		QKI	X		TMPO	X	
BCL2A1	X	X	DSTYK	X		IFFO1	X		MMP16	X		RAC2	X		TMPRSS3		X
BCL2L14	X		DVL2	X		IGFBP7	X		MOXD1	X		RASGEF1B	X		TMTC1	X	
BEND6	X		EBF1		X	IL12RB2	X		MPDZ	X		RASL10B	X		TNF	X	
BIRC3	X		EBI3		X	IL15RA	X		MPP2	X		RASSF4	X	X	TNFAIP3	X	
C15orf48	X		EDNRB	X	X	IL16	X		MRAS	X		RASSF5	X		TNFAIP8	X	
C3ARL1	X		EMILIN3	X		IL23A	X		MRC2	X		RASSF8	X		TNFRSF14	X	
C3orf18	X		ENOX1	X		IL24	X		MSI1	X		RBPMS2	X		TNFSF10	X	
C3orf70	X		EPHA3	X		IL32	X		MSRB3	X		RCN2	X		TNFSF13B		X
CACNA1G		X	EPHB3		X	IL4I1		X	MYH10	X		RCOR2	X	X	TRAF3IP3	X	
CALD1	X		EPHB3		X	IRF4	X		MYLK	X		RECK	X		TRPC1	X	
CAMK4	X		EPHB3		X	ISG15	X		NCKAP5L	X		REEP2	X		TRPV2	X	
CAND2	X		EPST11		X	ITGA10	X		NES	X		RENBP	X		TTC28	X	
CATSPER1	X		EVC	X		ITGA4	X		NEXMIF	X		RGS1	X		TUB	X	
CAVIN1	X	X	EVC2		X	ITGA9	X		NFASC		X	RHOJ	X		TUBA1A	X	
CBX1	X		EVI2A	X		ITGB3	X		NFATC2	X		RTL5	X		UNC13D	X	
CCDC136	X		EXTL2	X		ITGB4	X	X	NGFR	X	X	RUNX3	X		USP22	X	
CCDC80	X		FAM171A2	X		ITIH5	X		NLGN1	X		RUSC2	X		VASH1	X	
CCN2	X		FAM180B	X		ITK	X		NLGN2	X		S100A8	X		VAV1	X	

CD96	X		FAM78A	X		JAM3	X		NMI	X		SAL L2	X		VIM	X	
CDH19	X		FAT4		X	JAZF1	X		NPL	X		SCARA5	X		VIPR1	X	
CERKL	X		FBLN1	X		KANK2	X		NREP	X	X	SCARF2	X		VSIR	X	
CERS1	X		FBN1	X	X	KBTBD6	X		NRP2	X		SCML4	X		WARS1	X	
CHD3	X		FBXL7	X		KCNAB1	X		NRROS	X	X	SCRG1	X		WFDC1	X	
CHL1	X		FBXO17		X	KCNH2	X		NTN4	X		SGCA	X		WIPF1	X	
CHST10	X		FCER1G	X		KCNJ10	X		NUDT11	X		SGCD	X		WWTR1	X	
CHST11	X		FCGR2A	X		KCNJ4	X		NYNRIN	X		SH2D1B		X	XCL1	X	
CIITA	X		FCGR2B	X		KDR	X		OBSL1	X		SH2D1B		X	ZC3H12B	X	
CLEC12A	X		FCMR	X		KIF5A	X		P2RX7	X		SH3B P1	X		ZCCHC24	X	
CLEC1A		X	FCRLA	X		KIRREL1	X		PALM	X		SH3PXD2A		X	ZEB1	X	
CLEC4E	X		FERMT2	X		KLF8	X		PARD6G	X		SH3PXD2B	X		ZEB2	X	
CLEC7A	X		FGD1	X		KLHL29	X		PCDHB7	X		SHANK1	X		ZMYND15	X	
CLIC5	X		FGD3	X		KRBA1	X		PDEIC	X		SHC4	X		ZNF101	X	
CLIP4	X		FGFR1	X		KRT14	X		PDE7B	X		SHISA4	X				

[0326] Relationships between gene expression and compound sensitivity in relation to subtypes can be visualized and explored via clustering. Using the gene list and selected compounds as described above, both datasets can be clustered and plotted as a heatmap. Clustering using the training set of cell lines shows genes and compounds with potentially related pathways and mechanisms of action co-clustering (Figure 13). Mechanisms of action appear to have relationships with subtypes (Table 23), which were also observed in the test set of cell lines (Figure 14).

[0327] These results were also validated through application of methods described herein to datasets obtained from the Cancer Therapeutics Response Portal (CTRP), which provided data from a screen of cancer cell lines for small-molecule sensitivity (Seashore et al., Cancer Discov. 2015 Nov;5(11):1210-23). As described for the PRISM screen, correlation of compound sensitivity across the cell lines to the IM, MSL and M subtype was determined, as well as measurements of significance (p values and q values). q values were determined as described by John D. Storey, Robert Tibshirani, Statistical significance for genomewide studies, Proceedings of the National Academy of Sciences Aug 2003, 100 (16) 9440-9445 using the qvalue R package. Compound correlations where the correlation was negative, indicating sensitivity to the compound, and with a q value less than 0.05 were assessed. From this list of compounds, 83% produced comparable results in both the PRISM and CTRP assays, suggesting a high degree of confidence in observed correlations.

[0328] Similarly, the results from the PRISM screen which had a q value less than 0.05 and were also screened in the CTRP assay (N=10) were assessed. 90% of these gave comparable results in both assays. Compounds classified as inhibitors of EGFR were identified as highly significant in both the CTRP and PRISM screens. Tumors of the IM class were also identified as especially sensitive to certain EGFR inhibitors (e.g. lapatinib, canertinib, afatinib). Interestingly, several drugs in this class have shown to have immunomodulatory effects during cancer treatment (Griguolo, et al., J. Immunotherapy Cancer 7, 90 (2019); Tu et al., Cancer Res. 2021 Jun 15;81(12):3270-3282). suggests that patients with a tumor classified as IM by TNBCType (the 101 gene signature) might be candidates for this class of drug.

[0329] Among other things, the present example demonstrates that compounds may be classified by association with genes of particular subtypes (IM, MSL, M) in order to inform selection of one or more therapies. In some embodiments, a tumor sample (*e.g.*, obtained through liquid biopsy, tissue biopsy, etc.) may be assessed to determine expression level of one or more genes or miRNAs as described herein. In some embodiments, a tumor sample may be assessed for DetermaIO scoring. In some embodiments, selection of treatment with one or more compounds may be based upon DetermaIO score. For example, in some embodiments, one or more compound treatments may be selected due to increased sensitivity of a tumor sample to such treatment(s) depending on DetermaIO score. In some embodiments, one or more compound treatments may be selected due to increased sensitivity of a tumor sample to such treatment(s) depending expression levels of genes and/or miRNAs classified in a particular subtype (*e.g.*, IM, M, MSL).

[0330] In some embodiments, the present example demonstrates that certain compounds (*e.g.*, anti-VEGF compounds, vitamin D receptor inhibitors) may associate with the MSL subtype. In some embodiments, the present example demonstrates that certain compounds (*e.g.*, CSF1R inhibitors) may associate with the M subtype. In some embodiments, the present example demonstrates that certain compounds (*e.g.*, CD40 agonists) may associate with the IM subtype.

Example 16: Assessment of tumor immune signatures

[0331] The present Example, among other things, demonstrates that classifications provided herein can be correlated with tumor immune infiltrate types and may be utilized and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0332] Gene expression data sets from tumors in eighteen types (lung squamous cell, lung adenocarcinoma, breast, ovarian, kidney clear cell, head and neck, prostate, melanoma, colon, bladder, pancreas, kidney papillary, sarcoma, rectal, B cell lymphoma, kidney chromophobe, esophageal and stomach cancers) were downloaded from the US NIH Genomic Data Commons Portal (https://portal.gdc.cancer.gov/). Each tumor's gene expression data was processed identically. Experiment data downloaded from the NIH data repository was converted to a DGE list using the R (version 4.1.1) function SE2DGEList in the edgeR package. Duplicate genes were reduced to a single gene by selecting the gene with the maximum standard deviation across all samples in the data set. HUGO Gene

Nomenclature Committee (HGNC) names for each gene were added using the biomarRt package. Genes without a HGNC designation were removed from the analysis. Using TMM normalization in the EdgeR package, normalization factors were calculated, applied, and log2 transformed counts per million (cpm) were determined for each gene for each sample. The distribution of cpm and the standard deviation of genes across samples was plotted, and cutoffs determined to remove very low expressing genes. Samples were then renormalized using TMM after these genes were removed. Potential confounding effects due to the institution from which a tumor sample was acquired was addressed by removing batch effect based on the tissue source site using the EdgeR package. The normalized and batch corrected gene expression data sets were then combined into a 2/3 training, 1/3 test set with tumors balanced for tumor type between the two sets, without shared institutions between the two. This results in 4696 tumor samples in the training set, and 2195 samples in the test. This gene expression data set is referred to herein as TCGA18.

[0333] One set of immune cell signatures were created from defined mouse immune cell populations. Gene expression data from the ImmGen public consortium (www.immgen.org) was downloaded. These data are derived from defined and purified mouse cells using the ImmGen ULI GSE109125 data set. Gene names were translated into human homologs, and when duplicate genes were present, those with maximum standard deviation across all lines were selected. This list of genes was limited to those that were present in a list of 937 genes derived from an analysis of lung squamous, melanoma and sarcoma tumor gene expression data sets to allow for maximum diversity between clusters defined by the 101 gene signatures, resulting in 740 genes. A data set was created using these 740 genes and the normalized and batch corrected data from TCGA18. Using these data, gene expression of tumor samples were correlated with gene expression of the ImmGen cells. Principal components were calculated and plotted for these correlations. The first component largely defined a tumor vs purified cell signature, so was removed, and a new correlation value for all samples was determined, and the average of the correlations with the ImmGen samples for each class of ImmGen sample was calculated. The average expression of genes for each cluster was calculated as the "ImmGen corr subPC1" signature. The average expression of these signatures for all assayed cells is summarized by subtype (*e.g.*, IM, MSL, M) and tissue of origin (Table 27A).

[0334] Table 27A: Average signature expression by subtype (IM, M, MSL) and tissue of origin.

	ImSig score.B cells	ImmGen corr subPC1 B cell	community B cell	ImSig score.Macrophages	ImmGen corr subPC1 macrophage	community Macrophage M1 M2	ImSig score.T cells	ImmGen corr subPC1 alpha-beta T	ImmGen corr subPC1 gamma-delta T	ImmGen corr subPC1 activated T	community T cell 1	community T cell 2	community NK T
Bcell lymphoma													
IM	13.99	0.33	1.85	91.59	0.33	4.56	16.41	0.22	0.21	0.20	7.17	-0.63	4.05
bladder													
IM	14.90	0.26	4.21	132.09	0.33	2.93	22.00	0.25	0.25	0.24	-0.15	-0.54	2.08
M	8.66	0.27	3.19	52.38	0.31	1.07	9.80	0.26	0.25	0.23	-1.15	-0.68	-0.37
MSL	24.76	0.28	3.12	89.64	0.31	2.35	19.05	0.26	0.25	0.23	1.00	-0.59	1.08
breast													
IM	21.56	0.28	3.25	146.55	0.33	3.90	31.39	0.25	0.25	0.23	1.59	-0.51	3.13
M	11.21	0.28	2.44	64.94	0.32	2.37	10.20	0.25	0.25	0.22	-0.55	-0.78	0.50
MSL	13.07	0.28	2.27	88.10	0.32	2.93	14.94	0.25	0.25	0.23	0.25	-0.77	1.37
colon													
IM	13.95	0.27	3.28	98.69	0.32	2.38	17.38	0.26	0.25	0.23	0.10	-0.18	1.49
M	11.64	0.27	2.49	67.51	0.31	1.41	12.22	0.26	0.25	0.23	-0.91	-0.22	0.02
MSL	19.29	0.29	2.69	104.69	0.33	2.67	20.14	0.25	0.25	0.22	1.68	-0.19	1.61
esophageal													
IM	15.68	0.27	5.20	109.32	0.32	2.71	19.66	0.25	0.25	0.23	0.83	-0.53	1.97
M	11.49	0.27	4.77	70.13	0.32	1.60	12.24	0.26	0.25	0.23	-0.56	-0.82	0.15
MSL	16.25	0.29	4.14	91.97	0.31	2.60	17.62	0.25	0.25	0.23	1.31	-0.54	1.22
Head and neck													
IM	15.13	0.26	5.36	106.47	0.33	2.84	19.66	0.26	0.25	0.24	0.25	-0.92	2.42

M	11.44	0.27	4.89	56.19	0.32	2.06	8.91	0.26	0.25	0.23	-0.73	-1.12	0.65
MSL	13.76	0.28	4.30	120.33	0.34	3.64	19.08	0.25	0.24	0.22	0.60	-0.94	1.86
kidchrome													
IM	14.78	0.27	1.55	105.81	0.34	2.11	17.36	0.24	0.25	0.22	-1.31	-0.41	0.12
M	13.01	0.27	0.69	71.85	0.32	0.88	14.87	0.25	0.25	0.22	-2.14	-0.70	-1.38
MSL	13.73	0.27	1.50	89.61	0.33	1.87	16.55	0.25	0.25	0.23	-1.36	-0.63	-0.04
kidclear													
IM	14.82	0.26	2.40	126.93	0.34	3.83	21.97	0.24	0.25	0.23	-0.63	0.22	2.55
M	11.21	0.27	1.75	-5.30	0.30	1.69	0.43	0.25	0.25	0.23	-1.69	-0.68	-0.58
MSL	13.00	0.27	2.07	46.14	0.32	3.17	9.37	0.25	0.25	0.23	-0.91	-0.38	1.07
kidpap													
IM	15.25	0.26	3.09	117.09	0.38	3.25	19.70	0.23	0.24	0.21	-0.64	-0.33	1.57
M	10.99	0.26	2.23	40.49	0.35	1.76	10.78	0.24	0.24	0.21	-1.88	-0.40	-0.25
MSL	14.55	0.27	2.56	92.12	0.36	2.85	15.35	0.24	0.24	0.21	-0.54	-0.60	0.71
lungadeno													
IM	14.68	0.28	4.17	94.86	0.34	4.11	18.25	0.24	0.24	0.22	1.71	0.01	2.79
M	3.48	0.28	3.90	-17.12	0.32	2.54	0.53	0.25	0.24	0.22	-0.50	-0.27	0.41
MSL	13.14	0.29	4.13	89.84	0.35	3.95	13.65	0.24	0.24	0.21	1.34	0.03	1.92
lungsquamous													
IM	15.25	0.28	4.51	95.92	0.34	3.50	18.36	0.25	0.25	0.23	1.27	-0.23	2.34
M	8.30	0.28	4.13	38.77	0.33	2.36	6.46	0.25	0.25	0.22	0.09	-0.44	0.64
MSL	17.18	0.28	4.77	158.41	0.35	4.03	23.28	0.24	0.24	0.21	1.33	0.04	2.06
melanoma													
IM	27.16	0.27	1.43	171.98	0.34	3.93	34.49	0.25	0.25	0.23	1.73	-0.76	3.54
M	3.90	0.27	1.10	29.78	0.34	2.19	3.17	0.25	0.25	0.23	-0.98	-1.02	0.52
MSL	24.01	0.28	0.81	154.56	0.33	3.55	24.64	0.25	0.25	0.22	2.24	-0.90	2.79
ovarian													

IM	14.27	0.27	3.22	126.55	0.34	2.72	18.61	0.25	0.24	0.23	-0.29	-0.55	1.12
M	13.44	0.28	2.54	54.03	0.31	1.73	13.78	0.26	0.25	0.22	-0.77	-0.69	-0.53
MSL	18.81	0.28	3.20	117.54	0.33	3.37	22.76	0.25	0.25	0.23	0.81	-0.69	1.65
pancreas													
IM	31.96	0.28	4.36	132.17	0.34	3.95	23.59	0.24	0.24	0.22	1.57	0.06	2.52
M	-3.95	0.27	3.96	62.92	0.34	2.91	6.69	0.25	0.24	0.22	-0.57	-0.09	0.71
MSL	18.73	0.29	4.20	98.00	0.33	3.67	19.23	0.25	0.24	0.22	1.80	0.15	2.01
prostate													
IM	22.82	0.26	1.89	134.39	0.30	2.47	28.74	0.27	0.27	0.24	0.79	-0.61	2.39
M	12.38	0.26	0.75	80.21	0.29	0.72	13.37	0.27	0.27	0.24	-1.69	-0.93	-0.26
MSL	14.15	0.26	1.24	93.14	0.29	1.53	16.80	0.27	0.27	0.24	-0.57	-0.92	0.68
rectal													
IM	13.91	0.27	3.48	93.99	0.33	2.50	16.82	0.25	0.25	0.23	-0.18	-0.21	1.35
M	12.27	0.27	3.01	78.64	0.32	1.88	13.72	0.26	0.25	0.23	-1.17	-0.37	0.16
MSL	16.94	0.28	3.18	102.20	0.33	2.76	18.96	0.25	0.25	0.23	0.80	-0.41	1.40
sarcoma													
IM	20.94	0.26	1.33	260.61	0.36	4.72	45.67	0.24	0.24	0.23	-0.22	-0.48	3.43
M	10.79	0.26	0.20	9.32	0.32	2.00	5.84	0.25	0.25	0.23	-2.09	-0.74	-0.49
MSL	15.92	0.26	1.02	143.06	0.35	3.86	21.62	0.25	0.24	0.23	-0.80	-0.62	1.40
stomach													
IM	13.46	0.27	4.40	115.29	0.33	3.36	19.48	0.25	0.24	0.23	1.25	-0.32	2.56
M	2.29	0.27	3.94	41.90	0.32	2.22	6.69	0.25	0.25	0.23	-0.27	-0.52	0.84
MSL	22.74	0.28	3.98	84.03	0.31	3.15	17.62	0.25	0.25	0.23	2.05	-0.39	2.09

[0335] **Table 27A key**

Component	Class of signature	Cell type detected
ImSig score.B cells	ImSig	B cells
ImmGen corr subPC1 B cell	ImmGen vector with first principal component removed	B cells
community B cell	Community detection signature derived from known markers	B cells
ImSig score.Macrophages	ImSig	Macrophages
ImmGen corr subPC1 macrophage	ImmGen vector with first principal component removed	Macrophages
community Macrophage M1 M2	Community detection signature derived from known markers	Macrophages
ImSig score.T cells	ImSig	T cells
ImmGen corr subPC1 alpha-beta T	ImmGen vector with first principal component removed	T cells, specifically gamma-delta unactived T cells
ImmGen corr subPC1 gamma-delta T	ImmGen vector with first principal component removed	T cells, specifically alpha-beta unactived T cells
ImmGen corr subPC1 activated T	ImmGen vector with first principal component removed	T cells, specifically actived T cells
community T cell 1	Community detection signature derived from known markers	T cells, specifically a mixed T cell population
community T cell 2	Community detection signature derived from known markers	T cells, specifically a mixed T cell population
community NK T	Community detection signature derived from known markers	T cells, specifically a mixed T cell population

[0336] In addition to the ImmGen signatures, signatures were also created to identify sets of immune cells that could potentially infiltrate tumors together (*e.g.*, natural killer cells and T cells). The signature used genes known to be markers for diverse immune cell types. A list of genes known to be differentially expressed in immune cell types was prepared comprising information from published sources as well additional genes of interest (Table 27B). Gene expression data for the training sets of tumor types breast, ovarian, bladder, lung adenocarcinoma and lung squamous cell carcinoma were each individually scaled. These scaled data sets were then clustered using fclust, with k=15. Clusters of gene identified by this process were limited to genes whose expression was three standard deviations above the mean for all genes. Clusters were only selected for further use if they contained at least ten genes. These selected clusters for all five tumors were combined and then used to create a network using the igraph package in R. Clusters of genes were defined by the cluster_louvain function in igraph. Genes defined by the community detection method were annotated by their cluster name (Table 28), which was derived from an examination of the immune markers that contributed to each cluster. The average

expression of genes for each cluster was calculated as the community detection immune signature. The average expression of these signatures for all assayed cells is summarized by subtype (*e.g.*, IM, MSL, M) and tissue of origin (Table 27A).

[0337] Table 27B: List of genes comprising those differentially expressed in immune cell types in addition to other genes of interest.

Gene	Cell Type	Gene	Cell Type	Gene	Cell Type	Gene	Cell Type	Gene	Cell Type	Gene	Cell Type
ABCB1	Cancer stem cell	CD200R1	M2A macrophage	CXCL10	M1 macrophage	ICAM1	Endothelial cell	LCN2	Neutrophil	S100A4	Fibroblast
ABCB5	Cancer stem cell	CD209	Dendritic cell	CXCL10	M2D macrophage	icam1	N1 neutrophil	LGR5	Cancer stem cell	S100A8	Neutrophil
ABCG2	Hematopoietic stem cell	CD22	B cell	CXCL16	M2D macrophage	ICAM2	Endothelial cell	LRRC32	Regulatory T (Treg) cell	S100A9	Neutrophil
ACTA2	Fibroblast	CD24	B cell	cxcl16	N2 neutrophil	IFNG	T helper1 (Th1) cell	LRRC36	T helper17 (Th17) cell	SELE	Endothelial cell
ADGRE1	Macrophage	CD244	Natural killer cell	cxcl2	N2 neutrophil	IFNGR1	T helper1 (Th1) cell	LTA	T helper1 (Th1) cell	SELL	B cell
AFP	Cancer stem cell	CD28	T cell	CXCL8	Neutrophil	Il	Dendritic cell	LY9	B cell	SELP	Endothelial cell
ALCAM	Mesenchymal stem cell	CD34	Hematopoietic stem cell	cxcl8	N2 neutrophil	IKZF2	Regulatory T (Treg) cell	LYVE1	Endothelial cell	SIGLEC8	Eosinophil
ALDH1A1	Cancer stem cell	CD37	B cell	CXCR1	Neutrophil	il10	M2A macrophage	LYZ	Macrophage	SLAMF1	Hematopoietic stem cell
ANPEP	Mesenchymal stem cell	CD38	M1 macrophage	CXCR2	Neutrophil	il10	M2B macrophage	MCAM	Mesenchymal stem cell	SOCS3	M1 macrophage
ARG1	M2 macrophage	CD3D	Natural killer cell	CXCR3	T helper1 (Th1) cell	il10	M2C macrophage	MCL1	Hematopoietic stem cell	SOX2	Cancer stem cell
B3GAT1	Natural killer cell	CD3E	Natural killer cell	CXCR4	Hematopoietic stem cell	il10	M2D macrophage	MET	Cancer stem cell	ST6GAL1	B cell
BLNK	B cell	CD3G	Natural killer cell	CXCR5	B cell	il12a	M1 macrophage	MHC	Dendritic cell	STAB2	Endothelial cell
BMI1	Hematopoietic stem cell	CD4	Regulatory T (Treg) cell	DCLK1	Cancer stem cell	il12b	M2D macrophage	MME	Fibroblast	STAT3	T helper17 (Th17) cell
CASP3	Hematopoietic stem cell	CD40	B cell	DPP4	Cancer stem cell	IL13	T helper2 (Th2) cell	MME	Mesenchymal stem cell	STAT5A	Hematopoietic stem cell
CAV1	Fibroblast	CD40LG	B cell	ECSCR	Endothelial cell	IL17A	T helper17 (Th17) cell	MNDA	Neutrophil	STAT5B	Hematopoietic stem cell
CCL1	M2B macrophage	CD44	Mesenchymal stem cell	EGR2	M2 macrophage	IL18R1	T helper1 (Th1) cell	MPO	Neutrophil	TBX21	T helper1 (Th1) cell
CCL11	M1 macrophage	CD47	Cancer stem cell	EMCN	Endothelial cell	il1b	M1 macrophage	MRC1	M2 macrophage	TEK	Endothelial cell
ccl15	M1 macrophage	CD48	Hematopoietic stem cell	ENG	Mesenchymal stem cell	il1b	M2B macrophage	mrc1	M2A macrophage	TFRC	Mesenchymal stem cell
CCL17	M2A macrophage	CD5	T cell	ENTPD1	Regulatory T (Treg) cell	il1r1	M1 macrophage	MS4A1	B cell	TGFB1	Regulatory T (Treg) cell
ccl17	N2 neutrophil	CD5L	M2 macrophage	EPCAM	Cancer stem cell	il1r2	M2A macrophage	MS4A4A	M2 macrophage	TGFb1	M2A macrophage

CCL2	M1 macrophage	CD68	M1 macrophage	ERBB2	Mesenchymal stem cell	IL1RAP	Cancer stem cell	MUC1	Epithelial cell	tgfb1	M2C macrophage
ccl2	N2 neutrophil	CD69	B cell	EZH2	Cancer stem cell	IL1RN	Macrophage	MYB	Hematopoietic stem cell	tgfb1	M2D macrophage
CCL22	M2A macrophage	CD7	T cell	FAP	Fibroblast	il23a	M1 macrophage	MYC	M2 macrophage	TGM2	M2A macrophage
CCL24	M2A macrophage	CD70	T Cell	fas	N1 neutrophil	IL2RA	Regulatory T (Treg) cell	MYD88	Cancer stem cell	THBD	Endothelial cell
CCL3	M1 macrophage	CD74	B cell	FCER2	B cell	IL2RB	Natural killer cell	NANOG	Cancer stem cell	THY1	Mesenchymal stem cell
ccl3	N1 neutrophil	CD79A	B cell	FCGR1A	M1 macrophage	IL4	T helper2 (Th2) cell	NCAM1	Natural killer cell	TIGIT	Regulatory T (Treg) cell
ccl3	N2 neutrophil	CD79B	B cell	FCGR2A	M1 macrophage	IL5	T helper2 (Th2) cell	NCR1	Natural killer cell	TLR1	M2C macrophage
CCL4	M1 macrophage	CD80	M1 macrophage	FCGR2B	M1 macrophage	IL5RA	Eosinophil	NES	Cancer stem cell	TLR2	M1 macrophage
ccl4	N2 neutrophil	CD83	Dendritic cell	FCGR2C	M1 macrophage	IL6	M1 macrophage	NGFR	Mesenchymal stem cell	TLR4	M1 macrophage
CCL5	M1 macrophage	CD86	M1 macrophage	FCGR3A	M1 macrophage	il6	M2B macrophage	NKG7	Natural killer cell	TLR8	M2C macrophage
CCL5	M2D macrophage	CD86	M2B macrophage	FCGR3A	Natural killer cell	IL6R	Epithelial cell	NOS2	Epithelial cell	TNF	T helper1 (Th1) cell
CCL8	M1 macrophage	CD8A	CD8+ T cell	FCGR3B	Natural killer cell	IL6ST	Epithelial cell	nos2	M1 macrophage	TNF	M1 macrophage
ccl8	N2 neutrophil	CD9	Embryonic stem cell	FLOT2	Cancer stem cell	ITGA1	Mesenchymal stem cell	NT5E	Mesenchymal stem cell	tnf	M2B macrophage
CCR1	T helper1 (Th1) cell	CD93	Hematopoietic stem cell	FLT1	Endothelial cell	ITGA2	Regulatory T (Treg) cell	PAX5	B cell	tnf	M2D macrophage
CCR2	M2C macrophage	CDH1	Embryonic stem cell	FLT3	Hematopoietic stem cell	ITGA4	Mesenchymal stem cell	PDGFRA	Fibroblast	tnf	N1 neutrophil
CCR3	Eosinophil	CDH1	Epithelial cell	FLT4	Endothelial cell	ITGA5	Mesenchymal stem cell	PDGFRB	Fibroblast	TNFRSF13B	B cell
CCR4	T helper2 (Th2) cell	CDH5	Endothelial cell	FOXP3	Regulatory T (Treg) cell	ITGA6	Mesenchymal stem cell	PDPN	Endothelial cell	TNFRSF13C	B cell
CCR5	T helper1 (Th1) cell	CEACAM6	Cancer stem cell	FPR1	Neutrophil	ITGAE	Epithelial cell	PECAM1	Mesenchymal stem cell	TNFRSF18	Regulatory T (Treg) cell
CCR8	T helper2 (Th2) cell	CEACAM8	Neutrophil	FPR2	M1 macrophage	ITGAM	Neutrophil	PLVAP	Endothelial cell	TNFRSF1A	Mesenchymal stem cell
CD14	Macrophage	CHI3L1	M2 macrophage	FUT4	Neutrophil	ITGAV	Mesenchymal stem cell	PODXL	Embryonic stem cell	TP63	Cancer stem cell
CD158	Natural killer cell	CHIT1	M2 macrophage	FZD9	Mesenchymal stem cell	ITGB1	Mesenchymal stem cell	POU2AF1	B cell	TREM1	Macrophage
CD160	Natural killer cell	Class	Dendritic cell	GATA3	T helper2 (Th2) cell	KLF4	Cancer stem cell	POU2F2	B cell	VCAM1	Mesenchymal stem cell

CD163	M2 macrophage	CLEC4C	Dendritic cell	GFI1	Hematopoietic stem cell	KLRB1	Natural killer cell	POU5F1	Mesenchymal stem cell	VEGFA	Endothelial cell
CD163	M2A macrophage	CLEC7A	M2 macrophage	GLI1	Cancer stem cell	KLRC1	Natural killer cell	PROCR	Endothelial cell	VEGFa	M2D macrophage
CD163	M2C macrophage	CR2	B cell	GNG11	Endothelial cell	KLRD1	Natural killer cell	PROM1	Mesenchymal stem cell	VWF	Endothelial cell
CD19	B cell	CSF1R	Macrophage	GPR18	M1 macrophage	KLRK1	Natural killer cell	PTEN	Hematopoietic stem cell		
CD1A	Dendritic cell	CSF3R	Neutrophil	HAVCR2	T helper1 (Th1) cell	KRT18	Epithelial cell	PTGDR2	T helper2 (Th2) cell		
CD1C	Dendritic cell	CTLA4	Regulatory T (Treg) cell	HLA-ABC	Mesenchymal stem cell	KRT19	Epithelial cell	PTPRC	T cell		
CD1D	Epithelial cell	CTNNB1	Cancer stem cell	HLA-DR	Mesenchymal stem cell	KRT8	Epithelial cell	RETNLB	M2 macrophage		
CD2	T cell	cxcl1	N2 neutrophil	HLA-DRA	B cell	LAG3	Regulatory T (Treg) cell	RORA	T helper17 (Th17) cell		

[0338] Table 28: Genes defined by community detection method and annotated with cluster name.

Gene	Cluster	Gene	Cluster	Gene	Cluster	Gene	Cluster	Gene	Cluster	Gene	Cluster
PLVAP	endothelial	ENG	endothelial	TLR4	macrophage	CD3G	NK_T	KLRD1	NK_T	TNFRSF13C	B_cell
ECSCR	endothelial	MNDA	macrophage	CD14	macrophage	CD5	NK_T	NCR1	NK_T	FCER2	B_cell
GNG11	endothelial	CD86	macrophage	CD74	macrophage	LY9	NK_T	CD7	NK_T	POU2F2	B_cell
EMCN	endothelial	HAVCR2	macrophage	HLA-DRA	macrophage	SLAMF1	NK_T	CCR5	NK_T	CD22	B_cell
TEK	endothelial	FCGR2A	macrophage	IL2RA	macrophage	TIGIT	NK_T	CTLA4	NK_T	PTPRC	T_cell_plus
CD93	endothelial	FCGR1A	macrophage	CD209	macrophage	CCL4	NK_T	CXCR5	B_cell	LTA	T_cell_plus
CD34	endothelial	FCGR3A	macrophage	FPR1	macrophage	KLRK1	NK_T	MS4A1	B_cell	CCR4	T_cell_plus
CDH5	endothelial	CD4	macrophage	CD48	NK_T	GFI1	NK_T	PAX5	B_cell	CD28	T_cell_plus
PECAM1	endothelial	CCR1	macrophage	CD8A	NK_T	IL2RB	NK_T	CD79B	B_cell	CD40LG	T_cell_plus
VWF	endothelial	CD163	macrophage	TBX21	NK_T	NKG7	NK_T	CD79A	B_cell	FLT3	T_cell_plus
FLT4	endothelial	MS4A4A	macrophage	CXCR3	NK_T	CCL5	NK_T	POU2AF1	B_cell	KLRB1	T_cell_plus
CAV1	endothelial	CSF1R	macrophage	CD3D	NK_T	LAG3	NK_T	CD19	B_cell	CCR2	T_cell_plus
LYVE1	endothelial	TLR8	macrophage	CD2	NK_T	CXCL10	NK_T	TNFRSF13B	B_cell	CD37	T_cell_plus
LRRC32	endothelial	ITGAM	macrophage	CD3E	NK_T	IFNG	NK_T	CR2	B_cell		

[0339] A previously defined set of immune signatures was also employed (Nirmal et al., Cancer Immunol Res. 2018 Nov;6(11):1388-1400). TCGA18 gene expression samples were processed as described above, but without a log transformation, and the imsig package in R used to classify samples. These signatures for all assayed cells are summarized by subtype (e.g. IM, MSL, M) and tissue of origin (Table 27A).

[0340] These three sets of distinct signatures, designated as 'ImSig', 'ImmGen' and 'Community Detection', show considerable conservation, as seen in a high correlation between most signatures sharing a B cell, T cell, or macrophage target (Figure 15). As the community detection signatures identify sets of co-infiltrating immune cells, correlation of these signatures with multiple immune cell types may occur. The signatures were then used to classify clustered tumor expression data. Training data for lung adenocarcinoma and lung squamous cell tumors are shown (Figure 16 and Figure 17). In the lung adeno cluster the macrophage signature was strong for many of DetermaIO+/MSL cases and some also have T cell infiltrate signatures. B cell infiltrates appeared in other tumors, predominantly in the IM cluster. In the M cluster, there were a high number of un-activated T cell (as seen with the ImmGen ab and gd T cell signatures) infiltrates, while activated T cells (ImmGen activated T cell and ImSig and community detection T cell signatures) were mostly in IM. In the lung squamous cases, B cell infiltrates appeared rare outside of IM. However, distinct from lung adenocarcinoma cases, T cell infiltration was observed in IM and MSL, though high levels of un-activated T cells were still found in M.

[0341] Similar distributions of immune signatures were observed in the test set of cases for these same tumors, both lung adenocarcinoma (Figure 18) and lung squamous cell carcinoma (Figure 19). For both tumors, macrophage infiltration was observed frequently in IM and MSL cases, and un-activated T cell infiltration was predominantly in M cases, while activated T cell infiltration was in the IM cluster (and in lung squamous, also in MSL), as seen in the training data.

[0342] Among other things, the present example demonstrates that immune infiltrate information may be determined through analysis of gene expression data and correlated with various tumor and gene expression subtypes (*e.g.*, IM, M, MSL). In some embodiments, methods provided herein may be used to determine immune infiltrate levels for a particular tumor type without the need for a solid tumor biopsy. In some embodiments, immune infiltrate information may be used to inform or select one or more therapies for a tumor. In

some embodiments, immune infiltrate information may be used in combination with tumor gene expression subtype data and/or DetermaIO scoring to inform or select one or more therapies for a tumor. In some embodiments, immune infiltrate information may be used in combination with tumor gene expression subtype data and/or DetermaIO scoring to identify patients whose cancer may not be adequately met by existing therapeutic regimens, or otherwise are strong candidates for novel drug discovery and development programs.

Example 17: Scoring based upon gene methylation

[0343] The present Example, among other things, demonstrates that gene methylation status may be utilized in score prediction or other characterization of technologies as described herein (e.g., assessment of likely responsiveness to IO therap(ies), selection and/or modification of administered therap(ies) (including combination therap(ies)), monitoring of tumor development and/or evolution, etc).

[0344] Gene expression and gene methylation (Beta values – where beta 0 means unmethylated and beta of 1 means fully methylated) datasets for five cancers were downloaded from the genomic data commons (GDC) portal (https://portal.gdc.cancer.gov/) using the Genomic Data Commons package in R. Assessed cancers included Bladder Urothelial Carcinoma (BLCA), Breast invasive carcinoma (BRCA), Colon Adenocarcinoma (COAD), Lung Adenocarcinoma (LUAD), and Lung squamous cell carcinoma (LUSC). Subtype (IM, M, MSL) was calculated as previously described for each sample in the dataset. Cancer datasets (BLCA, BRCA, COAD, LUAD and LUSC) were then split, with 5% of each dataset reserved to create a small validation set (n=130) and 95% concatenated to create the training set (n=2026).

[0345] With the training set established, calculations were performed to generate the spearman rho correlation coefficient between between each gene's beta values across all samples and subtype (IM, M, MSL), yielding three spearman rho values. Spearman rho values with a p value of <.05 were removed from the set. Three lists of genes were generated containing 75 genes with the highest spearman rho in a corresponding subtype (*e.g.*, 75 genes for each of IM, M, and MSL). A total of 214 unique genes were obtained from this assessment. Genes whose methylation status (beta value) were highly correlated with a particular subtype (IM, M, MSL) were selected as described in Example 15 and are outlined in Table 29 below.

[0346] Table 29: Genes with particularly elevated methylation levels that correlate with a subtype (IM, M, MSL).

Gene	Subtype	Gene	Subtype	Gene	Subtype	Gene	Subtype	Gene	Subtype	Gene	Subtype	Gene	Subtype
TRAF1	M	APOBEC3A	MSL	BATF	M	GRB7	IM	BTN3A3	M	ACVR1	IM	C1orf150	MSL
S100A9	MSL	PCNAP1	M	LGALS9B	MSL	CD101	M	INPP5J	IM	MOBKL2A	M	CHML	M
CD3E	M	ATIC	MSL	MIR770	MSL	RARRES3	M	HIF1A	MSL	PRAME	MSL	C10orf91	MSL
HIST4H4	MSL	A2ML1	MSL	EPHA1	MSL	GSR	MSL	SLC25A15	IM	SLC44A2	IM	ZC3HAV1L	MSL
WARS	MSL	BST2	M	CNDP2	MSL	TSTD1	MSL	MPHOSPH9	M	MIR155	M	COMTD1	MSL
GRIK4	MSL	VAMP1	M	TM4SF1	MSL	HN1	MSL	UBE2L6	M	P4HA2	IM	GRIA1	MSL
MTMR11	IM	NME6	M	C17orf44	IM	BCL2L2	IM	UNC13C	MSL	WDR34	IM	NFU1	IM
RHOB	IM	CSNK1E	IM	CORO1A	M	CRB3	IM	C5orf56	M	VRK2	MSL	HLA-B	M
OAS2	M	C17orf87	M	MPL	IM	DCAF5	IM	LOC285692	MSL	MIR19B1	MSL	TTC33	MSL
RNF167	M	VAMP8	MSL	MIR92A1	MSL	TUBA1C	MSL	LOC648691	MSL	C15orf52	IM	GAPDH	MSL
RHBDL2	IM	RAB13	IM	MIR19A	MSL	PHKG1	IM	PLCD4	IM	OR2G3	MSL	SNORD93	MSL
C10orf107	IM	RAVER1	IM	SEC16B	MSL	GRHL2	MSL	FRK	IM	CRK	IM	PSMB8	M
HS1BP3	IM	RILP	IM	BCL9L	IM	SP140L	MSL	RAB19	MSL	MIR609	M	PTPN6	M
HLA-E	M	TNFSF8	M	SIT1	M	LNX1	MSL	TMEM159	IM	IGFBP4	IM	CLEC2D	M
IFNAR1	M	TMC6	M	ARNTL2	MSL	CHMP4C	MSL	C17orf91	IM	TEC	MSL	SLC2A1	MSL
RTKN	IM	ELOF1	M	BOK	IM	MGC3771	IM	ZC3HAV1	M	C2orf29	MSL	FAM96B	IM
ZNF641	IM	CD3D	M	CYP4F3	MSL	EVL	M	SNX11	M	RARA	IM	TNFSF12-TNFSF13	IM
TRIM69	M	PARP4	MSL	KSR1	MSL	LGALS8	IM	DEGS1	MSL	CDH1	IM	EVI2B	M
SPN	M	LOC257358	M	PTPRCAP	M	ROD1	MSL	RCAN3	M	MPZL2	IM	ACTR3C	MSL
AGAP2	IM	LTBR	IM	FNBP1	M	MIR142	M	ST7OT1	IM	SLPI	MSL		
LOC100131496	IM	CFLAR	M	RHOH	M	MMP14	IM	NLRC5	M	PRSS8	IM		
ESRP2	IM	DENND2D	M	S100A8	MSL	ASF1A	MSL	TAGAP	M	LOC400931	IM		
GGPS1	M	C11orf34	MSL	LOC150568	MSL	CST7	MSL	GPR65	M	LOC338799	IM		
HTATIP2	MSL	MIR18A	MSL	MIR1251	MSL	ACAP1	IM	CD2	M	KCTD11	IM		

SLA2	M	FASLG	M	GPD2	IM	TNFSF13	IM	TBC1D10C	M	TMEM149	M		
MAP1LC3B2	MSL	LOC100130776	IM	LTA	M	MIR17	MSL	GBP4	MSL	B2M	M		
MON1A	IM	DIABLO	M	STK38L	MSL	CTNND1	IM	BTLA	M	SLC25A23	IM		
ABHD10	IM	ADAM28	MSL	AGTRAP	IM	ST7OT4	IM	TEF	IM	CD52	M		
KDELR3	IM	C21orf15	MSL	HMGA1	MSL	LOC100233209	M	CORO1B	M	TNKS1BP1	IM		
SSH3	IM	ENO1	MSL	MIR22	IM	8-Sep	IM	MIR17HG	MSL	OCLN	IM		
TNFRSF10A	MSL	KRTDAP	MSL	TAP1	M	C14orf33	IM	AIP	M	SLC39A2	IM		
MIR20A	MSL	EVI2A	M	PAPPA2	MSL	FLJ13224	MSL	EIF2C4	IM	LAMB2	IM		
MIR1252	M	IRF1	M	CXCR6	M	PPP1R14B	IM	SUOX	IM	RAP1A	M		
GSDMC	MSL	LAX1	M	KMO	M	SYS1	M	MFSD6L	IM	DAPP1	MSL		

[0347] Among other things, the present Example demonstrates that available gene methylation data may be utilized, and, in some embodiments, combined with the 101 gene signature, to produce a model to classify genes with abnormally high methylation levels (*e.g.*, as compared to a reference) into a particular signature type (*e.g.*, IM, M, MSL). In some embodiments, this model may be used to assess a sample of interest (*e.g.*, tumor sample from a subject, blood and/or plasma sample from a subject) for gene methylation status (*e.g.*, relative to a reference) in order to assess IM, M, and MSL signature levels. In some embodiments, assessment of gene signature levels could be leveraged to create a gene methylation-specific scoring system to inform selection and/or modification of therapy (*e.g.*, ICI therapy, chemotherapy, etc.).

[0348] For example, in some embodiments, a tumor sample with one or more methylated genes correlating to a particular subtype (*e.g.*, M, MSL) could be treated with one or more therapies to reduce or inhibit methylation (*e.g.*, methyltransferase inhibitor, demethylase) and shift tumor status to a different subtype (*e.g.*, IM). In some embodients, one or mroe therapies to reduce or inhibit methylation (*e.g.*, methyltransferase inhibitor, demethylase) may be combined with one or more additional therapies (*e.g.*, ICI therapy, chemotherapy, etc.).

Example 18: Scoring based upon gene methylation

[0349] The present Example, among other things, demonstrates that classifications provided herein can be correlated with promoter and/or gene methylation and expression level and may be utilized for and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0350] Potential promoter regions were identified using R (version 4.2.1) and the package GenomicFeatures and the TxDb.Hsapiens.UCSC.hg19.knownGene annotation package, applied to breast cancer data was from the TCGA. Potential promoter regions 100 kb upstream from the start of gene were selected for further analysis. Methylation probes for the promoter regions of the genome were then selected.

[0351] Each individual tumor sample was mapped to one or more of the IM, M, and MSL subtypes as described herein. Samples were then grouped to perform three different sets of comparisons: Group 1) Samples with an IM subtype as compared to those with an M

or MSL subtype; Group 2) Samples with an IM subtype as compared to those with an MSL subtype; and Group 3) Samples with an MSL subtype as compared to those with an M subtype.

[0352] For each group, a logistic regression model was fit for each gene to identify candidate genes that could be drivers of transition from one immune state to another (e.g., IM to M / MSL or vice versa (Group 1 above), IM to MSL or vice versa (Group 2 above), M to MSL or vice versa (Group 3 above)). Each model used the promoter with largest standard deviation in methylation beta values as the feature to predict subtype. The p-value for the feature was stored for each of these models. A Benjamin-Hochberg correction was applied to select the "best" models. A linear regression model was then generated for each probe to predict gene expression based upon methylation value. These analyses were intended to confirm that methylation status of a promoter corresponds to expression of a potential target gene. Mean absolute percentage error (MAPE) was calculated and stored for each model. Genes whose MAPE was in the bottom quantile of each Group were kept for further analysis, as shown in Table 30, Table 31, and Table 32 below.

[0353] Table 30: Gene list produced after MAPE filtering of Group 1 genes.

Gene											
ARHGEF10	SLC2A7	SPATA5L1	ZNF230	TMEM30A	PIRT	HIVEP3	KIF22	CIZ1	COL15A1	HSP90AB1	RCOR3
TPRKB	MCM2	ANP32E	CXCR4	HIP1R	ITGA1	RAB17	OCIAD1	SPEM1	NDUFC2	UBLCP1	TXNRD1
SGSM2	KRT27	CDC42EP4	ANXA6	CRYZ	EVX2	ACP2	C1QC	HSD3B7	TTC14	CDYL	TRIM22
SKAP2	VGLL4	TGM7	SKA2	CASP2	MAD1L1	EID1	TNFAIP8L1	NUPR1	PSMG1	DDX1	XPO1
ZMIZ2	PYROXD1	CDK2AP1	GALNT11	SPRR2F	CKAP5	LAMB2	TSPAN4	NBL1	UBB	CALD1	SCLT1
DZIP3	GTF2H5	B4GALT2	POLL	KLHDC8B	B3GNT6	LPP	CDC25B	ATCAY	RRP7A	PPP1R15B	ARHGAP27
DNAJB12	TGFBI	RUNX1	ZC3H11A	TNFAIP2	SELENBP1	PLXDC2	FUT11	PARP14	MTUS1	TCF21	TMEM18
PELO	KHNYN	C1orf198	DDAH1	CD81	PPP2R2D	RALBP1	GPR137	ABHD12	TMX4	CEP97	CCNG1
GOLPH3L	NCK1	SEC14L1	RBMS2	TRAF3IP2	CSNK1A1L	LMO7	LPIN2	AP1M2	CFLAR	MTIF3	BCAP29
SLC25A46	RUSC1	SLC37A1	MON1A	LIMA1	ITPRIPL2	SLC29A1	GNB2	S100A16	TNS1	ETS1	HSD17B4
ALDH7A1	LAMA4	FKBPL	SIGIRR	SPARC	BBS7	RANBP1	DHCR24	MARVELD2	BAIAP2	LNX1	UBXN11
DIXDC1	TPM3	RAB11FIP3	LPAR2	EPB41L1	SLC33A1	MAP3K13	ESAM	SRRM1	NSMCE1	SCFD1	CASKIN2
ZNF562	CCDC86	AMPD2	TRIOBP	ZNF8	CYB5R4	MKS1	LGALS8	LMBRD1	EHD2	ZCCHC14	RPP30
HNRNPF	TRIB2	SULF2	NSUN5	MRPS27	NEU1	SYPL1	DCUN1D3	USP47	SH3YL1	RPS6KA1	TRAPPC9
ILVBL	ZNF207	RASA3	NCOR2	NDUFA6	EPHB4	CDK10	FOXRED1	PIGC	POLD2	KIAA1217	RIN2
FLII	TMEM63A	IFITM3	SH3BP2	USP6NL	TRIM4	ILF2	MYOF	NXPH2	WHAMM	DENND2D	THBS1
KDR	HSPA1B	UNC45A	ZNF440	ZNF581	SNX1	TNFSF12	MAP3K11	FRG1	LYPLAL1	SPRED2	LYN
C1RL	CYTH3	ANO6	LIMS1	CFL2	SOCS4	PPEF2	SRP19	SLMAP	ZNF320	GAB1	SNX25
MEF2D	TUT1	FKBP1A	MLH3	S100A10	ADAM18	ACVRL1	TCEA2	RNF34	VIM	ZSCAN29	TAF7
MTX3	SPATA13	IL17RC	MCM3AP	STK36	DNAJC14	GLUL	CD93	RAB11B	PURA	ABHD14B	TPRA1
COMT	PRDM7	C11orf58	OR2H2	PTP4A1	TMEM129	LARP1	DDR1	ZNF558	PHOX2A	TLE3	PTPRB
LAMB1	ZMYND8	SHROOM3	GGCT	PKN1	NDUFAF3	ASTE1	AGK	BTBD1	CRX	SEC13	PROM2
STT3A	FLAD1	FBXO6	TM9SF4	CDK5RAP1	INPP5A	AGPAT1	DPH2	HOOK1	TMBIM1	TMC4	DCTN3
YIPF3	BUD31	MGAT1	MBIP	NUFIP1	WIPF1	GNAI2	GPATCH3	IFI16	HTR6	FAM110A	GSTO1

FAM118A	ARCN1	GUSB	CAST	CCNL2	PLRG1	ZNF621	PSMD6	MKNK2	PNLIP	EIF5A	ECE1
PTER	ZDHHC13	SLC36A2	PRRG2	C10orf88	ACTL6A	TCF12	PELI1	RAI1	DSPP	RNF25	TBRG4
GSDMD	TRAK1	MRPS21	GPATCH8	HLCS	PDIA4	DUS1L	JARID2	KDM2B	YTHDF2	ANKRD11	POGZ
CARD8	PNPLA2	COX11	AK3	LDLR	NR2F2	BID	YWHAQ	USP33	PARP6	TRMT12	DTX3
LGALS3BP	GHITM	GPR152	JMJD1C	PSD4	NCOA4	AGPAT3	CLUAP1	WFDC10A	SCPEP1	LCN15	TMBIM4
ZBED5	GC	PGAP2	RARA	DAAM1	UBXN6	OR8A1	DNMT3A	IFT122	NBEAL2	HERC2	TIMP2
PXN	LMNA	WDR75	RUFY3	MAX	TMEM140	BCL9L	NDUFS2	RPL23A	CST3	PHACTR4	RBBP9
TNPO1	PALMD	NDUFS3	FAR1	PSMB7	GANC	APLP2	VARS2	INPP5B	RPS7	DNAJB1	TTC38
IRF6	ATP6V0A1	LBH	GMFB	NUCB1	ORAI3	APBB2	PTPRF	ALDOA	BCL9	TGFBR2	AP4S1
ARAP1	KBTBD4	C12orf40	RAPGEF1	CD44	MFN2	MLH1	B3GNT9	ZNF385A	RBM47	ZNF44	PKP3
SHMT2	FBXO40	BCR	CRTC2	TBC1D22B	ZMYND11	CABLES1	MGAT4B	OR10G2	DIP2C	FANCF	GALR3
YIPF5	AP2A2	RHOD	ZNF600	SPINK7	ROBO4	PSMC5	TXN2	PTPN6	ARHGEF10L	ALG10B	FFAR3
FSCN1	EPM2AIP1	GPS2	RAB4A	MUL1	ELOVL5	ZNF787	TTC27	BTNL2	NAGK	RPTOR	CRY2
FAM107B	TMC6	KRT8	PACSIN2	MGST2	PDCL3	SLC38A10	PLEKHA6	SMAD3	EPS8	NET1	MFSD1
NBR1	ITGB2	PPM1M	HSPA4	PPOX	GPN1	IRX5	TOMM40L	SMTN	TPM4	CCDC50	MAPK6
LGALS1	GOLIM4	SLC27A3	CLSTN1	COL1A1	PEX5	GORASP2	POLG2	USP54	NXNL1	KRT85	GSS
MARCKS	TFAP2A	ETS2	UBE2U	CRELD1	OTX2	SDC2	ATN1	UBA5	TNKS1BP1	CDK2	
NUDT16	CPT2	MORC1	BBX	PTPN12	FKBP10	MED18	KDM3B	SERPINB1	SLC12A4	KCTD12	
ZNF561	VGLL2	GRHL2	STAB1	TPM1	BCL2L13	AHSP	SCD	UBE2E1	PRKAG2	BTBD17	
C11orf24	MPZL3	MAF	SHC1	CD74	RNASEL	ISY1	SFTPA1	NUDT19	SLC44A2	SLC11A2	
CALHM2	MCRS1	ZNF358	FBXL19	LDHAL6B	ZNF639	STK38L	TKTL2	PTK2	MRPL9	PAPOLB	
WWTR1	CD5L	EPS8L2	RPS6KA2	ANKH	NUMA1	ARHGEF7	COASY	NME3	PAAF1	TNPO2	
SCOC	PPP1R9B	FAM111A	NUBP1	FAM193A	GH1	PARVA	EIF3E	WDR6	AMBRA1	TMEM69	
NSUN3	C15orf39	PTPRK	PGK2	TNIP2	OCIAD2	KNCN	RHOT2	POLR1C	RFFL	PDE8A	
WIPI2	FKBP14	BARHL2	HIPK1	DDX46	SYNPO	RPL32	STK16	UACA	PRCP	ABHD8	

[0354] Table 31: Gene list produced after MAPE filtering of Group 2 genes.

Gene												
TNPO1	LGALS3BP	NCOA4	DDX46	DNAJB12	SULF2	CST3	ZNF8	SOCS4	RAI1	FANCF	FKBP14
RALGAPB	SLMAP	DIXDC1	CABLES1	DZIP3	TNIP2	MAX	NUDT16	EPB41L1	PKN1	BCAP29	HIPK1
CRELD1	SHMT2	ZNF207	TXNRD1	CCDC86	NBEAL2	BAIAP2	NSMCE1	KDM3B	OCIAD1	SLC33A1	LIMS1
PSMB8	GSN	SLC27A3	PARP14	PPEF2	CD5L	PMP22	MYOF	POLD2	ETS2	GAB1	FMOD
RHOD	PNPLA2	ARCN1	MGST2	SEC13	ELOVL5	COMT	ZNF26	ILVBL	TRAK1	MKNK2	KIAA1217
CTRL	SMAD3	FBXO38	ZNF558	RPL23A	DCUN1D4	HOOK1	RAB4A	DTX3	ASB5	TMBIM4	AP1M2
ZNF600	CARD8	PSMD5	CRX	RFFL	SPRR2F	RAPGEF1	SPATA13	NUDT19	TPRKB	IPO5	ZMYND11
ALDH4A1	LDHAL6B	PGAP2	TAF7	NUCB1	FBXL19	COX8A	LGALS1	MUL1	IL17RC	KRT27	BCL9
DCUN1D3	LPIN2	ZNF358	ANKRD11	MARVELD2	PIRT	ZNF518A	PRRG2	GORASP2	DUS1L	FSCN1	RIN2
PPP2R2D	DDR1	PSMC5	VGLL2	TMEM140	TCN2	SHROOM3	NDUFA6	LIMA1	B4GALT2	SCFD1	PPP1R15B
ARAP1	RNASEL	ANXA6	APC	LPAR2	TRAF3IP2	FKBPL	TTC14	SLC25A46	TMEM63A	EHD2	ZMIZ2
KRT8	THBS1	CDK2	CALD1	EID1	HERC2	TCEA2	PXN	TGFBI	CRY2	TGM7	PSMB7
C1QC	DDAH1	HIVEP3	HLCS	GPATCH8	DCTN1	PALMD	ACVRL1	CD74	IRF6	ZC3H11A	GPATCH4
DNAJC14	ZNF621	PARVA	BCL2L13	PDIA4	POLG2	TSKU	NUPR1	RNF34	CD93	APLP2	RARA
TNFAIP8L1	ABHD14B	FBXO40	SLC24A5	TNFSF12	AP4S1	SELENBP1	SYPL1	CCNDBP1	RUSC1	TGFBR2	MRPL3
BCR	AXL	TMX4	FKBP10	MAD1L1	SKA2	ALDH7A1	SEC14L1	TRIM4	STK36	MAP3K11	SPEM1
TLE3	BRD9	C15orf39	TMEM30A	FFAR3	HIP1R	BTBD17	KIF22	NCK1	EIF3E	NFATC4	GNAI2
CDK10	ABRA	FAM107B	PTGR1	TBRG4	CALHM2	SPG21	CXCR4	STK38L	UBE2U	ZNF44	KLHDC8B
ANP32E	ITGB2	DSPP	KBTBD4	SPARC	PRDM7	TRIOBP	EVX2	TMC6	NXNL1	POLR1C	TMC4
GSTO1	PPFIBP2	FOXE3	MGAT1	ATCAY	GOLIM4	RALGDS	UACA	BID	PTPRF	RAB17	ZNF561
BUD31	MPZL3	TUT1	CCNL2	ZNF385A	UBE2E1	PELI1	ZSCAN29	PARP6	ARHGEF10L	NBR1	WDR6
TKTL2	SLC29A1	ORAI3	HTR6	NDUFAF3	ATN1	NDUFS3	PSD4	BMF	RPS6KA1	STT3A	ZBED5
RAB11FIP3	CD44	PPM1M	ITPRIPL2	PROM2	PPP1R9B	SPATA5L1	MCRS1	BBS7	INPP5A	COX11	MCM2
EPHB4	NXPH2	LAMB2	NAGK	SERPINB1	CYTH3	AP2A2	DHCR24	BCL9L	ALG10B	C11orf24	RCOR3
YTHDF2	NDUFS2	PTPN6	ISY1	TOMM40L	OR2H2	LYN	WWTR1	PDE8A	CDK2AP1	FXYD5	SH3YL1
GRAMD4	MEF2D	FAM110A	PAPOLB	ZNF787	KDM2B	TRIO	C11orf58	EIF5A	RBMS2	OR10G2	TNFAIP2
ALDOA	GRHL2	USP47	CEP97	TIMP2	RBM47	LMBRD1	PSMD6	ITGA1	SLC37A1	DCTN3	PDCL3

ALX3	TNFRSF1B	GUSB	ATM	LBH	SGSM2	SNX1	TMEM129	SPRED2	JMJD1C	ARHGEF7	PRKAR2A
XPO1	RASSF1	NET1	LYPLAL1	MLH3	TNPO2	LOXL1	USP54	GMFB	SIGIRR	COL15A1	PTPRB
COASY	TCF21	RBM5	CRYZ	ALCAM	FOXRED1	DENND2D	RPS7	WIPI2	VIM	PPOX	TMEM18
C1RL	MTIF3	CD81	SLC36A2	POLL	IFITM3	MTUS1	VARS2	PTER	ZNF581	GH1	SLC11A2
ACTL6A	PHACTR4	AHSP	EPHX1	HSP90AB1	FLII	SRP19	UBB	SLC12A4	CIZ1	WFDC10A	FAM118A
STAB1	TRIB2	CFL2	GALR3	TSC22D1	RALBP1	KNCN	GC	COL1A1	NUBP1	MKS1	AMPD2
GPS2	LMNA	ACP2	NEU1	SLC44A2	USP6NL	TXN2	PEX5	GANC	LMO7	IFT122	GSDMD
HSPA1B	LAMA4	SLC38A10	ATP4B	LARP1	ILF2	PRCP	NUMA1	SYNPO	APBB2	PSMG2	
BARHL2	TRIM22	TPM1	SLC2A7	C1S	TBC1D22B	ZMYND8	CCNG1	CDC42EP4	GOLPH3L	ZNF639	
SH3BP2	PGK2	PIGC	KCTD12	NID1	CDYL	NR2F2	TRMT12	PKP3	RPS6KA2	DDX1	
PURA	SCPEP1	TPRA1	CPT2	BTBD1	PSMG1	TPM4	LGALS8	ESAM	PRKAG2	AMBRA1	
PELO	MRPS27	TSPAN4	WHAMM	TFAP2A	AK3	MYL9	GPR142	HPCAL1	PTPN12	ANKH	
SFTPA1	FUT11	ABHD12	ZCCHC14	S100A13	RPP30	GALNT11	TPM3	NDUFC2	MAP3K13	UBA5	
L3MBTL2	SCLT1	CRTC2	RRP7A	LDLR	IFI16	ZDHHC13	S100A10	CASKIN2	SNX25	TTC27	
OTX2	ATP6V0A1	GSS	LCN15	MMRN2	PLEKHA6	RANBP1	USP33	MED18	YIPF3	DIP2C	
PNLIP	HSPA4	UBLCP1	UBXN11	RASA3	RUNX1	CSNK1A1L	YWHAQ	KNG1	MRPL9	AGPAT3	
OR8A1	MON1A	YIPF5	ANO6	CKAP5	MGAT4B	VGLL4	CFLAR	RUFY3	GHITM	PAAF1	
JARID2	PTPRK	PTK2	MTX3	RFPL1	DNMT3A	GGCT	FAM193A	BANF1	UNC45A	PLXDC2	
MORC1	AGPAT1	ZNF562	AGK	C1orf210	TARBP2	CDK5RAP1	RPTOR	LUZP1	NSUN3	NCOR2	
ACACA	DNAJB1	RNF25	SPINK7	LHX5	BBX	FAM111A	SHC1	B3GNT6	ST7	ZNF529	
ZNF721	FLAD1	CAST	KHNYN	ETS1	TTC38	COL6A3	ZNF320	KRT85	LNX1	CLUAP1	
GTF2H5	TMBIM1	TNKS1BP1	EPS8L2	INPP5B	UBXN6	KDR	IRX5	C1orf198	ADAM18	CDC25B	

ARRDC2	PXN	WSB1	PDE7A	S100A13	HECW2	DDX1	TMEM30A
BCAS3	BRD4	ZNF350	SLC38A8	HEXA	CABLES1	HPCAL1	GRHL2
ZNF560	ZNF254	MORC2	STK38L	NME2	YTHDF2	GPRC5C	SSH1
DNAJB12	PPFIBP2	AMIGO3	COX7C	SFXN1	FLII	GORASP2	HNF1B
OR10G2	SIAH1	TJAP1	RNF34	PARVB	DNAJC5	CD81	ALDH7A1
STK19	KIR3DX1	RGS16	TTC1	MFSD1	CD93	ZNF320	IL10RB
ECE1	MGST2	ZNF621	AHR	PDXK	CYB561	RPS7	TCF12
BRD9	NEURL4	S100A6	NUCB1	ATP6V0A1	PSMG1	DENND2D	GSN
RALGDS	PTGS1	HSP90AB1	GTSF1L	NIPA1	FURIN	RBM19	FBXO6
TSTD1	CCNDBP1	ANO6	OCIAD2	ITPR3	LMBRD1	ZNF544	UBE2E1
BMF	SELENBP1	MMRN2	PELI1	SLC25A2	EIF5A	GALR3	KDM3B
TMCO1	PSG3	GRAMD4	TJP2	SIRT6	ZNF44	FAM174B	TXNIP
SHC1	ICA1	GOLIM4	RAB11FIP3	KPRP	RAB4A	FXYD5	CCDC88A
UBXN6	RAB11B	C10orf105	C12orf40	NRP2	MYL12A	RPL10L	THBS3
CCDC50	POGZ	ABCG1	ZNF440	RASA3	FKBP10	MEF2D	ALDOA
C1orf198	TGFBR2	CKAP5	RNASEL	MRPL3	TRERF1	IFT122	CCDC86
ATM	AIPL1	ILVBL	TAF7	MNAT1	WDR82	ZMIZ2	ZNF430
ZFP41	GNAI2	AP2A2	ZNF787	CCDC149	SYPL1	FAM118A	SRC
GNB2	PNLIP	TBRG4	PHACTR4	PRKACA	ST7	GBX1	SETMAR
FSCN1	CTRL	CDYL	RNF220				

[0356] The UniProt web API was then searched for genes from the analyses above (Table 30, Table 31, Table 32) with an associated keyword of "disease variant," with results shown in Table 33, Table 34, and Table 35 below. Additionally, the Targetome database was utilized to determine which identified genes are also targets for one or more cancer therapies, as shown in Table 36, Table 37, and Table 38 below. Genes that contained the keyword of interest or were in the Targetome database were identified as genes of high interest for potential modulators of the immune state transition.

[0357] Table 33: Gene list produced after keyword filtering of Group 1 genes.

Gene							
ARHGEF10	AMPD2	CSNK1A1L	FOXRED1	CRX	TNPO2	MLH1	KRT8
TPRKB	GUSB	BBS7	MAP3K11	HTR6	MAPK6	IRX5	GRHL2
SLC25A46	SLC36A2	SLC33A1	DDR1	PNLIP	GSS	STK38L	MAF
ALDH7A1	CXCR4	NEU1	AGK	DSPP	PTK2	DNMT3A	FAM111A
KDR	TRIOBP	EPHB4	DPH2	PPP1R15B	POLR1C	NDUFS2	RARA
COMT	SH3BP2	NDUFAF3	GPATCH3	RPS6KA1	CST3	VARS2	FAR1
STT3A	MLH3	ACTL6A	CIZ1	GAB1	PRKAG2	IRF6	RPS6KA2
CARD8	TRAF3IP2	NR2F2	HSD3B7	EIF5A	HERC2	SHMT2	HIPK1
MCM2	SPARC	LAMB2	ATCAY	ANKRD11	POLG2	YIPF5	MAX
PYROXD1	EPB41L1	MAP3K13	ABHD12	TXNRD1	ATN1	NSUN3	PSMB7
GTF2H5	NDUFA6	MKS1	PIGC	HSD17B4	KDM3B	WIPI2	PPOX
TGFBI	CFL2	ACVRL1	RAB11B	LYN	SFTPA1	GC	COL1A1
LAMA4	STK36	GLUL	MKNK2	ECE1	COASY	LMNA	CRELD1
TPM3	PKN1	TCF12	NDUFC2	POGZ	STK16	ITGB2	PTPN12
TMEM63A	HLCS	KIF22	RRP7A	TGFBR2	IFT122	TFAP2A	TPM1
FLAD1	LDLR	C1QC	MTUS1	NET1	ALDOA	CPT2	ANKH
TRAK1	MAD1L1	LPIN2	VIM	KRT85	SMAD3	PGAP2	MFN2
PNPLA2	B3GNT6	GNB2	PURA	CDK2	UBA5	NDUFS3	ROBO4
RUNX1	SELENBP1	DHCR24	PHOX2A	SLC11A2	GH1	BCR	ELOVL5
PEX5	OTX2	FKBP10					

[0358] Table 34: Gene list produced after keyword filtering of Group 2 genes.

Gene							
CRELD1	PNPLA2	NET1	RRP7A	CST3	CXCR4	B3GNT6	TGFBR2
PSMB8	SMAD3	CFL2	AGK	MAX	DHCR24	KRT85	MAP3K11
ALDH4A1	CARD8	TPM1	MAD1L1	PMP22	VARS2	PKN1	POLR1C
KRT8	LPIN2	PIGC	SPARC	COMT	GC	TRAK1	STT3A
C1QC	DDR1	ABHD12	ATCAY	SELENBP1	PEX5	TPRKB	PPOX
BCR	AXL	GSS	NDUFAF3	ALDH7A1	TPM3	TMEM63A	GH1

EPHB4	ITGB2	YIPF5	MLH3	TRIOBP	IRX5	IRF6	MKS1
ALDOA	NDUFS2	PTK2	C1S	NDUFS3	EPB41L1	STK36	IFT122
ALX3	GRHL2	TXNRD1	TFAP2A	LYN	KDM3B	RPS6KA1	ANKH
COASY	LMNA	CRX	LDLR	TRIO	SLC25A46	VIM	UBA5
ACTL6A	LAMA4	ANKRD11	ELOVL5	MTUS1	TGFBI	CIZ1	HIPK1
SH3BP2	FLAD1	APC	TRAF3IP2	NR2F2	STK38L	RPS6KA2	PPP1R15B
PURA	FBXO38	HLCS	HERC2	CSNK1A1L	BBS7	PRKAG2	PSMB7
SFTPA1	PGAP2	FKBP10	POLG2	FAM111A	EIF5A	PTPN12	RARA
OTX2	CDK2	HTR6	ATN1	COL6A3	WIPI2	MAP3K13	MRPL3
PNLIP	DSPP	ATM	TNPO2	KDR	COL1A1	NSUN3	MCM2
GTF2H5	FOXE3	SLC36A2	FOXRED1	NDUFA6	NDUFC2	SLC33A1	SLC11A2
SHMT2	LAMB2	NEU1	RUNX1	ACVRL1	KNG1	GAB1	AMPD2
GSN	GUSB	CPT2	DNMT3A	KIF22	BANF1	MKNK2	

[0359] Table 35: Gene list produced after keyword filtering of Group 3 genes.

Gene				
BCAS3	SELENBP1	SIRT6	MORC2	SLC38A8
ECE1	RAB11B	MRPL3	HECW2	STK38L
TMCO1	POGZ	PRKACA	DNAJC5	AHR
ATM	TGFBR2	GRHL2	CYB561	
GNB2	AIPL1	HNF1B	EIF5A	
TJP2	PNLIP	ALDH7A1	FKBP10	
RPL10L	HEXA	TCF12	ALDOA	
IFT122	PDXK	GSN	SRC	
SIAH1	NIPA1	KDM3B	RNF220	

[0360] Table 36: Gene list filtering Group 1 genes for those identified as targets for one or more cancer therapies.

Gene						
KDR	PKN1	ACVRL1	MKNK2	LYN	PTK2	RARA
COMT	CSNK1A1L	C1QC	HTR6	TGFBR2	STK16	RPS6KA2
CXCR4	EPHB4	MAP3K11	RPS6KA1	CDK2	STK38L	HIPK1
STK36	MAP3K13	DDR1	TXNRD1	MAPK6	BCR	PSMB7

[0361] Table 37: Gene list filtering Group 2 genes for those identified as targets for one or more cancer therapies.

Gene						
PSMB8	DDR1	TXNRD1	LYN	CXCR4	RPS6KA1	TGFBR2
C1QC	AXL	HTR6	CSNK1A1L	STK38L	RPS6KA2	MAP3K11

BCR	CDK2	C1S	KDR	PKN1	MAP3K13	HIPK1
EPHB4	PTK2	COMT	ACVRL1	STK36	MKNK2	PSMB7
RARA						

[0362] Table 38: Gene list filtering Group 3 genes for those identified as targets for one or more cancer therapies.

Gene		
TGFBR2	SRC	AHR
PRKACA	STK38L	

[0363] In some embodiments, the present example demonstrates that methylation status of certain genes and/or gene promoters may increase IM, M, and/or MSL character of a tumor. In some embodiments, changes in methylation status (*e.g.*, increased or decreased methylation) of certain genes and/or gene promoters may drive a change in subtype character of a tumor. In some embodiments, changes in methylation status (*e.g.*, increased or decreased methylation) of certain genes and/or gene promoters may drive a change from M and/or MSL subtype to IM subtype. In some embodiments, a treatment may be selected to produce changes in methylation status for certain genes and/or gene promoters , for example in order to increase or decrease methylation of genes associated with IM (*e.g.*, potentially increasing IM subtype character of a tumor and/or DetermaIO scoring).

Example 19: Assessment of data from miRNA targeting exemplary gene sets

[0364] The present Example, among other things, demonstrates that classifications provided herein can be correlated with pre-miRNA expression data and utilized for and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0365] A list of pre-miRNAs was generated as outlined in Example 13 above (see Table 14). Expression levels of miRNAs of interest were used to build a linear regression model predicting continuous DetermaIO score. An optimal threshold was calculated using an f-1 score curve to see if such continuous scores could be mapped to a binary DetermaIO call. With a threshold of .021, a precision of 80% was achieved on the validation set and 75% for the blind test set when using expression of selected pre-miRNA to predict mRNA expression-based DetermaIO call (Figure 20, parts A-B). The same process was repeated for the list of mature miRNAs previously described in Example 13 above (see Table 21B).

[0366] miRNAs of interest were also entered into the IntAct database from EMBL EBI. Results were filtered to show entries in which interation was between an miRNA of interest and genes of interest disclosed in the present application. Another filtering step narrowed the list to include either: 1) immune "cold" miRNAs (mapping to an M or MSL subtype) that interact with an immune "hot" gene (mapping to an IM subtype); or 2) immune "hot" miRNAs (mapping to an IM subtype) that interact with an immune "cold" gene (mapping to an M or MSL subtype). Resulting miRNAs of interest are outlined in Table 39 below.

[0367] Table 39: Hot and cold miRNA / gene interaction pairs.

Alias(es) interactor A	Alias(es) interactor B	Interaction type(s)
hsa-mir-29a-3p	mrna_igf1	psi-mi:"MI:0915"(physical association)
mrna_igf1	hsa-mir-142-5p	psi-mi:"MI:0915"(physical association)
mrna_zeb2	hsa-mir-142-3p	psi-mi:"MI:0915"(physical association)
mrna_zeb2	hsa-mir-142-3p	psi-mi:"MI:0915"(physical association)
hsa-mir-155-5p	mrna_zeb2	psi-mi:"MI:0915"(physical association)

[0368] In some embodiments, a tumor sample (*e.g.*, obtained through liquid biopsy, tissue biopsy, etc.) may be assessed to determine expression level of one or more classified pre-miRNAs as described herein. In some embodiments, treatments targeting or inhibiting miRNAs (*e.g.*, pre-miRNAs, mature miRNAs, combinations thereof) classified under a different subtype as compared to one or more target genes could produce a shift in mRNA levels for said one or more target genes, resulting in changes in tumor signatures and/or IO scoring. For example, in some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) classified as one subtype (*e.g.*, M, MSL) targeting a gene classified as a different subtype (*e.g.*, IM) could produce an increase in overall IM signature for a tumor and result in an increased IO score. In some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) classified as one subtype (*e.g.*, IM) targeting a gene classified as a different subtype (*e.g.*, M, MSL) could produce an increase in overall M or MSL signature for a tumor and result in a decreased IO score. In some embodiments, information obtained from miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) assessment can be used to inform treatment decisions – e.g., selection and/or modification of therapy. In some particular embodiments, information obtained from miRNA (*e.g.*, pre-miRNA, mature

miRNA, combinations thereof) assessment can be used to inform selection and/or modification of combination therapies (e.g., additional therapy in combination with ICI therapy). In some embodiments, information obtained from matched data sets can be used to inform selection and/or modification of therapies, and in particular of combination therapies (e.g., additional therapy in combination with ICI therapy) based upon changes in IO scoring. In some embodiments, treatment targeting or inhibiting miRNA (*e.g.*, pre-miRNA, mature miRNA, combinations thereof) could be combined with one or more therapies (*e.g.*, chemotherapy, ICI, etc.) based upon changes in IO scoring.

Example 20: Assessment of interactions within exemplary gene sets

[0369] The present Example, among other things, demonstrates that gene/gene interactions may be assessed within exemplary gene sets generated through methods disclosed herein in order to determine respnosiveness to therapy and/or select one or more therapies.

[0370] A set of genes generated through centroid modeling methods disclosed herein and in Example 11 were entered into the IntAct database from EMBL EBI. Results were filtered to generate a list of gene interactions and then further filtered to produce a list of interactions between an immune "hot" (IM) and immune "cold" (M, MSL) gene. These interactions are outlined in Table 40 below.

[0371] In some embodiments, gene interactions (*e.g.*, between an immune "hot" and immune "cold" gene as described herein) may inform selection of one or more therapies. For example, in some embodiments, increased expression of an immune "cold" (M, MSL) gene with a known interaction with an immune "hot" (IM) gene may inform selection of one or more therapies intended to suppress the immune "cold" gene. In some embodiments, one or more therapies intended to supporess the immune "cold" gene may be combined with another therapy (*e.g.*, ICI therapy). In some embodiments, increased expression of an immune "cold" (M, MSL) gene with a known interaction with an immune "hot" (IM) gene may be combined with DetermaIO scoring to inform selection of one or more therapies (*e.g.*, ICI therapy).

[0372] Table 40: Hot and cold gene interaction pairs.

Alias(es) interactor A	Alias(es) interactor B	A Phe no	B Phe no	Alias(es) interactor A	Alias(es) interactor B	A Phe no	B Phe no	Alias(es) interactor A	Alias(es) interactor B	A Phe no	B Phe no	Alias(es) interactor A	Alias(es) interactor B	A Phe no	B Phe no	Alias(es) interactor A	Alias(es) interactor B	A Phe no	B Phe no
FYB1	FYN	Hot	Cold	GAB3	DLG4	Hot	Cold	BEND5	RTP5	Cold	Hot	RPRM	CD33	Cold	Hot	ESR1	XRN1	Cold	Hot
ABL1	HCK	Cold	Hot	DLG4	IRF7	Cold	Hot	TXLNB	LPXN	Cold	Hot	FXYD6	FPR2	Cold	Hot	PIAS3	APOE	Cold	Hot
PLCG1	AGAP2	Cold	Hot	SP100	CBX5	Hot	Cold	KANK2	ABI3	Cold	Hot	CNIH2	CD53	Cold	Hot	STK4	FYN	Hot	Cold
HCK	ELMO1	Hot	Cold	LDOC1	IKZF3	Cold	Hot	RBPMS	DOK3	Cold	Hot	KANK2	RHOH	Cold	Hot	LAT	ITPR1	Hot	Cold
RCN2	TRAF1	Cold	Hot	ADA	SGCD	Hot	Cold	MEOX2	DOCK8	Cold	Hot	RPRM	CD53	Cold	Hot	PTPRC	CASQ2	Hot	Cold
GTF2I	NFKB2	Cold	Hot	CRYAB	CCL22	Cold	Hot	SAMD3	LMO3	Hot	Cold	RPRM	SUSD3	Cold	Hot	PTPRC	PLCG1	Hot	Cold
BCL7A	RELB	Cold	Hot	P2RX7	EFNB3	Hot	Cold	RBPMS	FOXP3	Cold	Hot	KIF3C	STK4	Cold	Hot	EPHB3	CD14	Cold	Hot
FYN	CD2	Cold	Hot	IRF2	FKBP7	Hot	Cold	CARD9	MEOX2	Hot	Cold	SMAP2	SMAD9	Hot	Cold	SH2D2A	GTF2I	Hot	Cold
CD2	FYN	Hot	Cold	IL23A	ESR2	Hot	Cold	MEOX2	GPSM3	Cold	Hot	MEOX2	BTK	Cold	Hot	ITK	PLCG1	Hot	Cold
LEPR	JAK3	Cold	Hot	GFI1	PIAS3	Hot	Cold	TRAF1	AQP1	Hot	Cold	LAT	GRAP	Hot	Cold	SYDE1	LYN	Cold	Hot
LEPR	JAK2	Cold	Hot	PIAS3	GFI1	Cold	Hot	RTP5	RBPMS	Hot	Cold	LAT	TLN1	Hot	Cold	STAP1	CDO1	Hot	Cold
CLNK	FYN	Hot	Cold	LCP2	PLCG1	Hot	Cold	LZTS2	CARD9	Cold	Hot	LAT	FYN	Hot	Cold	STAT1	LMOD1	Hot	Cold
LYN	EFS	Hot	Cold	GRIP1	AGAP2	Cold	Hot	ESR1	NFKB2	Cold	Hot	LCP2	GRAP	Hot	Cold	TXK	CDO1	Hot	Cold
ABL1	DOK2	Cold	Hot	AGAP2	GRIA1	Hot	Cold	ESR1	FAS	Cold	Hot	CD36	TLR6	Cold	Hot	ZAP70	CDO1	Hot	Cold
DOK2	ABL1	Hot	Cold	AGAP2	GRIP1	Hot	Cold	ESR2	NFKB2	Cold	Hot	TLR4	TLR6	Cold	Hot	SOCS1	RCN2	Hot	Cold
SMAD9	ASB2	Cold	Hot	CD14	FSTL1	Hot	Cold	AIM2	RCN2	Hot	Cold	CD36	LYN	Cold	Hot	HCK	CHD3	Hot	Cold
BTK	GTF2I	Hot	Cold	DHX58	AGO2	Hot	Cold	AIM2	FOXC1	Hot	Cold	C1QA	HSPB2	Hot	Cold	DOK2	FLNA	Hot	Cold
GTF2I	BTK	Cold	Hot	AGO2	DHX58	Cold	Hot	AIM2	GTF2I	Hot	Cold	KCNA5	KCNA3	Cold	Hot	DOK2	SPIN1	Hot	Cold
DLG4	KCNA3	Cold	Hot	FMNL1	FMNL3	Hot	Cold	AIM2	BEND3	Hot	Cold	LSP1	TMOD1	Hot	Cold	LRCH2	DOCK8	Cold	Hot
KCNA3	DLG4	Hot	Cold	FZD8	C1QA	Cold	Hot	MNDA	RCN2	Hot	Cold	BATF3	RTL6	Hot	Cold	FOXP3	ZEB2	Hot	Cold
NCF4	HDAC4	Hot	Cold	C1QA	FZD1	Hot	Cold	MNDA	DHX57	Hot	Cold	BATF3	NPTX2	Hot	Cold	HTRA1	HTRA4	Cold	Hot
MRC1	BTK	Cold	Hot	C1QA	FZD7	Hot	Cold	ESR1	STAT1	Cold	Hot	CD79A	TTC28	Hot	Cold	HTRA4	TGFB3	Hot	Cold
CBX1	BTK	Cold	Hot	C1QA	FZD8	Hot	Cold	FOXP3	NOVA2	Hot	Cold	LAMP3	SYNM	Hot	Cold	WFS1	BATF	Cold	Hot
EFS	LYN	Cold	Hot	C1QA	FZD4	Hot	Cold	FOXP3	BEND3	Hot	Cold	LAMP3	ARL10	Hot	Cold	WFS1	GPSM3	Cold	Hot

CHD3	PSME1	Cold	Hot	VCAM1	TLN1	Hot	Cold	FOXP3	NOVA1	Hot	Cold	ICAM1	FOXF1	Hot	Cold	WFS1	TLR10	Cold	Hot
BEND5	GRAP2	Cold	Hot	VCAM1	FLNA	Hot	Cold	FOXP3	FOXP2	Hot	Cold	ICAM1	TTC28	Hot	Cold	NCBP3	PSME1	Cold	Hot
RBPMS	GRAP2	Cold	Hot	VCAM1	FLNC	Hot	Cold	MAX	WIZ	Hot	Cold	CYTIP	HBB	Hot	Cold	GLIS2	IL27	Cold	Hot
TIFA	DVL2	Hot	Cold	VCAM1	QKI	Hot	Cold	FOXP3	FOXP1	Hot	Cold	STX11	KIF7	Hot	Cold	KLF2	IL32	Cold	Hot
IFFO1	ACAP1	Cold	Hot	VCAM1	HIP1	Hot	Cold	FGD1	TAP2	Cold	Hot	CARD8	SALL2	Hot	Cold	GLIS2	IL32	Cold	Hot
KCNJ4	IL16	Cold	Hot	VCAM1	MYH10	Hot	Cold	MYH10	LYN	Cold	Hot	CARD8	PEAK1	Hot	Cold	MAX	TNFSF12	Hot	Cold
GAS7	FMNL1	Cold	Hot	FYB1	PLCG1	Hot	Cold	FYCO1	DDX60	Cold	Hot	CARD8	LRCH2	Hot	Cold	TIFAB	ACTN1	Hot	Cold
CSF1	MYH10	Hot	Cold	WIPF1	ROBO4	Hot	Cold	NLRP3	CBX5	Hot	Cold	BIN2	AMPH	Hot	Cold	HDAC4	ABI3	Cold	Hot
IKZF1	PIAS3	Hot	Cold	FUT8	GCH1	Cold	Hot	FOXO1	FOXP3	Cold	Hot	CD1B	NRSN2	Hot	Cold	HDAC5	FMNL1	Cold	Hot
IKZF1	ULK1	Hot	Cold	STAT1	KIT	Hot	Cold	NINL	ARRB2	Cold	Hot	VNN2	GPM6A	Hot	Cold	CNR2	RCN2	Hot	Cold
FYN	HCLS1	Cold	Hot	PLCG1	HCK	Cold	Hot	NINL	XRN1	Cold	Hot	VNN2	APOD	Hot	Cold	PI16	TRPV2	Cold	Hot
MX1	TRPC6	Hot	Cold	TEAD3	FAS	Cold	Hot	IL10	MEF2D	Hot	Cold	VNN2	FZD7	Hot	Cold	ABL1	TCL1A	Cold	Hot
TRPC6	MX1	Cold	Hot	DOCK8	LRCH2	Hot	Cold	MAF	IL10	Cold	Hot	HTRA4	TTC28	Hot	Cold	FGR	APOD	Hot	Cold
TRPC1	MX1	Cold	Hot	CBX1	MAX	Cold	Hot	PLCG1	CD244	Cold	Hot	MMRN1	APOE	Cold	Hot	LATS2	HERC6	Cold	Hot
QKI	HCLS1	Cold	Hot	ARRB2	SMO	Hot	Cold	CD244	PLCG1	Hot	Cold	LPXN	LPP	Hot	Cold	CPEB1	XRN1	Cold	Hot
SHC3	DOK2	Cold	Hot	RUNX3	HDAC4	Hot	Cold	RAB37	RAB3C	Hot	Cold	LPXN	MIB1	Hot	Cold	CPEB1	SMAP2	Cold	Hot
PLCG1	LCP2	Cold	Hot	RUNX3	HDAC5	Hot	Cold	LATS2	GRAP2	Cold	Hot	LPXN	CEP68	Hot	Cold	IRF1	BCL7A	Hot	Cold
IGKC	CAV1	Hot	Cold	HDAC4	RUNX3	Cold	Hot	DVL2	GRAP2	Cold	Hot	FGL2	FUT8	Hot	Cold	IRF4	CIC	Hot	Cold
WIPF1	DLG4	Hot	Cold	HDAC5	RUNX3	Cold	Hot	DVL2	TIFA	Cold	Hot	FGL2	KIF7	Hot	Cold	IRF4	BCL7A	Hot	Cold
ENAH	ABI3	Cold	Hot	AGO2	HERC6	Cold	Hot	GRAP2	LATS2	Hot	Cold	ESR1	GBP1	Cold	Hot	IRF4	MEF2D	Hot	Cold
IGHM	HBB	Hot	Cold	ESR2	IL24	Cold	Hot	GRAP2	DVL2	Hot	Cold	XCL1	FSTL1	Hot	Cold	IRF8	CIC	Hot	Cold
IGHG1	LTBP4	Hot	Cold	CAV1	NCF1	Cold	Hot	MEOX1	PARVG	Cold	Hot	ICAM3	FUT8	Hot	Cold	IRF8	BCL9	Hot	Cold
IGHG1	ELN	Hot	Cold	LCK	KIT	Hot	Cold	LPXN	TNS2	Hot	Cold	S1PR1	CD69	Cold	Hot	IRF8	FLI1	Hot	Cold
IGHG1	FGFR1	Hot	Cold	KIT	ZAP70	Cold	Hot	FOSB	FOXP3	Cold	Hot	FLNA	ARRB2	Cold	Hot	KLF8	MAX	Cold	Hot
MAX	EPAS1	Hot	Cold	KIT	FGR	Cold	Hot	TRAF1	CRY2	Hot	Cold	PLCG1	ITK	Cold	Hot	STAT4	ALMS1	Hot	Cold
FYN	LAT	Cold	Hot	HSH2D	KIT	Hot	Cold	GPR25	VAPB	Hot	Cold	ARRB2	EDNRA	Hot	Cold	STAT4	BCL7A	Hot	Cold
LAT	PLCG1	Hot	Cold	KIT	HCK	Cold	Hot	AXIN2	STX11	Cold	Hot	EDNRA	ARRB2	Cold	Hot	FGFR1	SMAP2	Cold	Hot
TLR4	LY96	Cold	Hot	STAP1	KIT	Hot	Cold	DLG2	AOAH	Cold	Hot	TAL1	LYL1	Cold	Hot	SKAP1	FYN	Hot	Cold

LY96	TLR4	Hot	Cold	KIT	LCK	Cold	Hot	IKZF3	HSPB7	Hot	Cold	JAK2	LEPR	Hot	Cold	CTLA4	FYN	Hot	Cold
ABL1	ACAP1	Cold	Hot	KIT	HSH2D	Cold	Hot	CD53	CD302	Hot	Cold	FNBP1	WIPF1	Cold	Hot	C1QA	LRP1	Hot	Cold
ABL1	P2RX7	Cold	Hot	LYN	KIT	Hot	Cold	RPRM	FGD2	Cold	Hot	AQP1	CD47	Cold	Hot	ADCY2	ARRB2	Cold	Hot
ABL1	FYB1	Cold	Hot	TXK	KIT	Hot	Cold	STX11	SHC3	Hot	Cold	CCL22	CCL14	Hot	Cold	STK4	MAP1B	Hot	Cold
WIPF1	FYN	Hot	Cold	BLK	KIT	Hot	Cold	TIFA	KANK2	Hot	Cold	ISG15	SYNM	Hot	Cold	BTK	FLNA	Hot	Cold
JAK2	PLCG1	Hot	Cold	KIT	LYN	Cold	Hot	CD33	RPRM	Hot	Cold	DLG4	AGAP2	Cold	Hot	BTK	ACTN1	Hot	Cold
AGO2	ZBP1	Cold	Hot	GRAP2	KIT	Hot	Cold	FPR2	FXYD6	Hot	Cold	AGAP2	DLG4	Hot	Cold	IFIT2	RCN2	Hot	Cold
AGO2	HERC5	Cold	Hot	HCK	KIT	Hot	Cold	CD79A	APOD	Hot	Cold	AGAP2	NUMBL	Hot	Cold	DLG4	SYTL3	Cold	Hot
ARRB2	MYH10	Hot	Cold	KIT	GRAP2	Cold	Hot	IL21R	AQP1	Hot	Cold	AGAP2	ANK2	Hot	Cold	HCLS1	DLG4	Hot	Cold
ARRB2	FLNA	Hot	Cold	ZAP70	KIT	Hot	Cold	CD53	CNIH2	Hot	Cold	AGAP2	SOGA1	Hot	Cold	RUNX3	DLG4	Hot	Cold
ARRB2	MAP1B	Hot	Cold	CLNK	PTK7	Hot	Cold	RHOH	KANK2	Hot	Cold	AGAP2	ACTN1	Hot	Cold	FRMD6	IKZF1	Cold	Hot
ARRB2	SPIN1	Hot	Cold	MPEG1	TNS2	Hot	Cold	CD53	RPRM	Hot	Cold	AGAP2	VAPB	Hot	Cold	FOXP3	RBPMS	Hot	Cold
ARRB2	BSN	Hot	Cold	STK4	ACACA	Hot	Cold	CD79A	AQP1	Hot	Cold	AGAP2	TLN2	Hot	Cold	MEOX2	CARD9	Cold	Hot
FGF2	CASP1	Cold	Hot	STK4	PAK3	Hot	Cold	CD79A	VAPB	Hot	Cold	AGAP2	DCLK1	Hot	Cold	CARD9	LZTS2	Hot	Cold
STK4	LATS2	Hot	Cold	STK4	GTF2I	Hot	Cold	CD79A	CNIH3	Hot	Cold	AGAP2	MAP6	Hot	Cold	PARVG	MEOX2	Hot	Cold
LATS2	STK4	Cold	Hot	WIPF1	ABI2	Hot	Cold	CD79A	WFS1	Hot	Cold	AGAP2	ENAH	Hot	Cold	GPSM3	MEOX2	Hot	Cold
PTPRC	TIE1	Hot	Cold	MEOX2	STX11	Cold	Hot	CD53	APOD	Hot	Cold	IFIH1	WIZ	Hot	Cold	ABI2	WIPF1	Cold	Hot
GHR	PTPRC	Cold	Hot	LZTS2	LCK	Cold	Hot	SUSD3	CNIH3	Hot	Cold	AGTR1	ABI3	Cold	Hot	STX11	MEOX2	Hot	Cold
PTPRC	LEPR	Hot	Cold	ATF7	FCER2	Cold	Hot	BACH2	BATF3	Cold	Hot	AGTR1	CD37	Cold	Hot	LCK	LZTS2	Hot	Cold
PTPRM	LCK	Cold	Hot	AQP1	TRAF1	Cold	Hot	IKZF3	KANK2	Hot	Cold	CCR4	RTN1	Hot	Cold	AQP1	IKZF3	Cold	Hot
LCK	PTPRG	Hot	Cold	IKZF3	AQP1	Hot	Cold	TRAF1	KANK2	Hot	Cold	AGTR1	ARRB2	Cold	Hot	TXLNB	TCL1A	Cold	Hot
PTPRB	LCK	Cold	Hot	BLK	EFS	Hot	Cold	TRAF1	SHC3	Hot	Cold	NCBP3	BST2	Cold	Hot	PARVG	MEOX1	Hot	Cold
DLG4	JAK3	Cold	Hot	TCL1A	TXLNB	Hot	Cold	LZTS2	TNIP3	Cold	Hot	NCBP3	CSF1	Cold	Hot	TNS2	LPXN	Cold	Hot
SLA2	SYNM	Hot	Cold	RTP5	BEND5	Hot	Cold	KCNA1	APOL2	Cold	Hot	FYN	FLT3	Cold	Hot	FOXP3	FOSB	Hot	Cold
AGAP2	MPRIP	Hot	Cold	RBPMS	RTP5	Cold	Hot	KLHL6	CRY2	Hot	Cold	ABL1	FLT3	Cold	Hot	CRY2	TRAF1	Cold	Hot
BTK	RFTN1	Hot	Cold	LZTS2	RTP5	Cold	Hot	LPXN	AQP1	Hot	Cold	APOE	LRP1	Hot	Cold	BATF3	BACH2	Hot	Cold
LCP2	FYN	Hot	Cold	LPXN	TXLNB	Hot	Cold	CD69	RPRM	Hot	Cold	DDX60	RCN2	Hot	Cold	KANK2	TRAF1	Cold	Hot
PLEK	ACTN1	Hot	Cold	NMI	TXLNB	Hot	Cold	ABI3	NHSL2	Hot	Cold	DDX60	SYNC	Hot	Cold	SHC3	TRAF1	Cold	Hot

HDAC5	MAX	Cold	Hot	TXLNB	NMI	Cold	Hot	KCNA3	KCNA1	Hot	Cold	IRF7	MAP1B	Hot	Cold	AQP1	LPXN	Cold	Hot
MMP9	ERG	Hot	Cold	AEI3	KANK2	Hot	Cold	ISLR2	NKG7	Cold	Hot	MX1	LRP4	Hot	Cold	RPRM	CD69	Cold	Hot
SVIL	MYO1G	Cold	Hot	DOK3	RBPMS	Hot	Cold	SUSD3	RPRM	Hot	Cold	NOD2	MYL9	Hot	Cold	KCNA1	KCNA3	Cold	Hot
ESR1	LACTB	Cold	Hot	NATD1	IKZF3	Cold	Hot	FPR2	APOD	Hot	Cold	NOD2	MYL3	Hot	Cold	SHC3	STX11	Cold	Hot
ESR2	LACTB	Cold	Hot	DOCK8	MEOX2	Hot	Cold	CD79A	HACD4	Hot	Cold	OAS3	TLN1	Hot	Cold	CNR2	CNR1	Hot	Cold
ESR2	ASB2	Cold	Hot	LMO3	SAMD3	Cold	Hot	SIT1	ITM2A	Hot	Cold	OASL	DHX57	Hot	Cold	CNR1	CNR2	Cold	Hot
FSTL1	CD14	Cold	Hot	IKZF1	LMO3	Hot	Cold	VAPB	GPR25	Cold	Hot	VAMP5	SYNPO	Hot	Cold	ESR1	PREX1	Cold	Hot
PLCG1	LAT	Cold	Hot	TNIP3	LZTS2	Hot	Cold	CD302	CD53	Cold	Hot	APBB1	MEI1	Cold	Hot				
FNBP1	ADAM8	Cold	Hot	PILRA	PIANP	Hot	Cold	PRKN	FAS	Cold	Hot	APBB1	WDFY4	Cold	Hot				
ADAM8	SNX33	Hot	Cold	SNX33	ADAM8	Cold	Hot	LRP1	APOE	Cold	Hot	DTNA	PLCB2	Cold	Hot				

Example 21: Assessment of tumor immune infiltrate signatures

[0373] The present Example, among other things, demonstrates that classifications provided herein can be correlated with tumor immune infiltrate types and may be utilized and/or included in assessments of subjects and/or their immune statuses and/or responsiveness to therapy.

[0374] *Preparation of RNASeq datasets*

[0375] Gene expression data sets from tumors in twenty tissue types (lung squamous cell, lung adenocarcinoma, breast, ovarian, kidney clear cell, head and neck, prostate, melanoma, colon, bladder, pancreas, kidney papillary, sarcoma, rectal, B cell lymphoma, kidney chromophobe, esophageal, stomach cancers, thymoma, and acute myeloid leukemia) were downloaded from the US NIH Genomic Data Commons Portal (https://portal.gdc.cancer.gov/). Additionally, murine RNAseq data from the ImmGen projects GSE109125 (Yoshida, Lareau et al. 2019) and GSE122108 (ImmGen 2016) were downloaded. The first dataset, GSE109125, are primary RNAseq data for 103 highly purified immunocyte populations representing all lineages and several differentiation cascades, profiled using the ImmGen ULI pipeline. The second dataset, GSE122108 are primary RNASeq data for progenitor, resident, and stimulated (C.alb, LPS, injury, APAP+ starved overnight and pIC) mononuclear phagocytes from fourteen organs.

[0376] Each tumor's gene expression data was processed identically. Experiment data was converted to a DGE list using the R (version 4.1.1) function SE2DGEList in the edgeR package(Robinson, McCarthy et al. 2010). Duplicate genes were reduced to a single gene by selecting the gene with the maximum standard deviation across all samples in the data set. Mouse gene names were converted to human orthologs using biomaRt(Durinck, Spellman et al. 2009). When there was gene duplication in orthologs, the gene with greatest homology with a human ortholog was retained. HUGO Gene Nomenclature Committee (HGNC) names for each gene were added using the biomarRt package. Genes without a HGNC designation were removed from the analysis. Using TMM normalization in the EdgeR package, normalization factors were calculated, applied, and log2 transformed counts per million (cpm) were determined for each gene for each sample. The distribution of cpm and the standard deviation of genes across samples was plotted, and cutoffs determined to

remove very low expressing genes. Samples were then renormalized using TMM after these genes were removed.

[0377] Potential confounding effects due to the institution from which a tumor sample was acquired was addressed by removing batch effect based on the tissue source site using the EdgeR package. To combine the two ImmGen datasets, each was batch corrected in edgeR, but finding no differences in models created using batch corrected and unaltered expression data, no batch correction was employed for final models using ImmGen data. The normalized and batch corrected gene expression human data sets were randomly combined into a 2/3 training, 1/3 test set with tumors balanced for tumor type between the two sets, without shared institutions between the two. This resulted in 4696 tumor samples in the training set, and 2195 samples in the test set. This gene expression data set is referred to herein as TCGA20.

[0378] *Creation of ImmGen-derived signatures*

[0379] One set of immune cell signatures was created from defined mouse immune cell populations. Gene expression data from the ImmGen public consortium (www.immgen.org) was downloaded. These data are derived from defined and purified mouse cells using the ImmGen ULI GSE109125 and GSE122108 data sets. Gene names were translated into human homologs, and when duplicate genes were present, those with maximum standard deviation across all lines were selected. To allow the applicability of models created using the ImmGen data to human tumors, this list of genes was limited to those that were present in both the TCGA20 and ImmGen dataset (N=14,611). Genes were further limited to those that Ensembl had scored as having a high confidence for the orthology (mmusculus homolog orthology confidence = 1), resulting in 14094 genes. ImmGen cell populations were grouped according to cell type, and also subdivided based on tissue of origin to identify potentially novel molecularly physiologically defined subtypes via k-means clustering, with k being determined with factoextra (Kassambara and Mundt 2020) using the elbow method (within total sum of squares). An elastic net (Friedman, Hastie et al. 2010) was used with lambda being set so that models contain at least five genes (unbounded on the upper end). The selected genes and coefficients for these models are shown in Table 41A.

[0380] Table 41A: Immune infiltrate model genes.

Model names	Model description	Gene Names	Gene coefficients	Model names	Model description	Gene Names	Gene coefficients	Model names	Model description	Gene Names	Gene coefficients
abT	alpha beta T cells	(Intercept)	2.001435055	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	GGCT	-0.146509	Macrophage_Brain	Macrophage cells with brain tissue origins	SALL1	0.0265053
abT	alpha beta T cells	AGFG2	0.02817566	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	HELZ2	-0.141925	Macrophage_Brain	Macrophage cells with brain tissue origins	SLCO1C1	-0.073116
abT	alpha beta T cells	ARHGEF11	-0.127029452	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	HS3ST3B1	-0.082309	Macrophage_Brain	Macrophage cells with brain tissue origins	SNAP25	0.0906954
abT	alpha beta T cells	ATF6	-0.036109757	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	KLHL33	0.1253497	Macrophage_Brain	Macrophage cells with brain tissue origins	SPOCK2	-0.161885
abT	alpha beta T cells	BBC3	-0.046892288	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	LMTK2	-0.474807	Macrophage_Brain	Macrophage cells with brain tissue origins	TAGLN3	0.0898985
abT	alpha beta T cells	CCDC186	-0.277005348	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	MOG	0.0144396	Macrophage_Brain	Macrophage cells with brain tissue origins	VTN	-0.157918
abT	alpha beta T cells	DNAAF4	0.010442018	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	NOL10	-0.00831	Macrophage_Heart	Macrophage cells with heart tissue origins	(Intercept)	-3.391014
abT	alpha beta T cells	DRC7	0.228172052	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	PHYKPL	-0.208104	Macrophage_Heart	Macrophage cells with heart tissue origins	ACTC1	0.1507811
abT	alpha beta T cells	EGLN2	-0.025400659	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	PTK2B	-0.22175	Macrophage_Heart	Macrophage cells with heart tissue origins	AREG	0.0735382
abT	alpha beta T cells	ESM1	0.126208896	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	REPS2	0.0618522	Macrophage_Heart	Macrophage cells with heart tissue origins	FOSL1	0.044466
abT	alpha beta T cells	FBXO4	-0.020497817	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	SH3GL1	0.2562942	Macrophage_Heart	Macrophage cells with heart tissue origins	HLA-DRA	0.2742392
abT	alpha beta T cells	HDAC9	-0.12708357	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	SMPD3	0.0281673	Macrophage_Heart	Macrophage cells with heart tissue origins	LSMEM1	0.0824488
abT	alpha beta T cells	IL2RA	0.003309983	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	SNX6	0.0488675	Macrophage_Heart	Macrophage cells with heart tissue origins	TNNC1	0.3733761
abT	alpha beta T cells	KCNH2	0.162758024	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	SORBS1	-0.112206	Macrophage_Liver	Macrophage cells with liver tissue origins	(Intercept)	-5.754201
abT	alpha beta T cells	KLC3	0.139619461	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	STK40	-0.277894	Macrophage_Liver	Macrophage cells with liver tissue origins	AASS	0.5996662
abT	alpha beta T cells	LYPD6B	0.128050897	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	USP16	-0.128092	Macrophage_Liver	Macrophage cells with liver tissue origins	C6	0.1840223
abT	alpha beta T cells	MC1R	0.065291376	Macrophage_clus6	Macrophage cells, k-means defined cluster 6	WWP1	0.559664	Macrophage_Liver	Macrophage cells with liver tissue origins	CD207	0.0004984
abT	alpha beta T cells	NCMAP	0.307146288	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	(Intercept)	-0.842026	Macrophage_Liver	Macrophage cells with liver tissue origins	CDH5	0.1824303
abT	alpha beta T cells	PLEKHA7	0.160165673	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	ANKRD12	-0.918137	Macrophage_Liver	Macrophage cells with liver tissue origins	CLEC4G	0.0398063
abT	alpha beta T cells	SOX13	-0.028158057	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	ATP13A5	-0.264776	Macrophage_Liver	Macrophage cells with liver tissue origins	FGG	0.3530157

abT	alpha beta T cells	TEDDM1	0.000519815	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	CAPN1	-0.105234	Macrophage_Liver	Macrophage cells with liver tissue origins	SERPINA1	0.2808324
abT	alpha beta T cells	TMEM106B	-0.376396054	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	CDC26	0.1433384	Macrophage_Liver	Macrophage cells with liver tissue origins	SMC1B	0.2803812
abT	alpha beta T cells	TRAT1	0.104222021	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	FOXRED2	-0.010795	Macrophage_Lung	Macrophage cells with lung tissue origins	(Intercept)	0.3288313
abT	alpha beta T cells	TRAV22	0.320717609	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	H4C14	-0.034928	Macrophage_Lung	Macrophage cells with lung tissue origins	B3GNT7	0.1271161
abT	alpha beta T cells	TRBV12-4	0.158582519	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	HAPLN1	0.1492342	Macrophage_Lung	Macrophage cells with lung tissue origins	CHD5	0.0546691
abT	alpha beta T cells	TRBV28	0.603361788	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	HPCAL4	0.0032812	Macrophage_Lung	Macrophage cells with lung tissue origins	FLVCR2	0.1739783
abT	alpha beta T cells	TRBV30	0.255161162	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	HSPB3	0.6597222	Macrophage_Lung	Macrophage cells with lung tissue origins	ITPR3	-0.156732
abT	alpha beta T cells	TRIM26	-0.091774153	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	KLF2	-0.043163	Macrophage_Lung	Macrophage cells with lung tissue origins	KLHL33	0.2293481
abT	alpha beta T cells	TRPA1	0.134336354	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	MTDH	0.3174562	Macrophage_Lung	Macrophage cells with lung tissue origins	LBH	-0.349301
abT	alpha beta T cells	WFIKKN2	-0.100872871	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	PLEKHG3	-0.273146	Macrophage_Lung	Macrophage cells with lung tissue origins	MFAP4	0.2702648
abT	alpha beta T cells	WNK3	-0.014812825	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	SNAP25	0.1833946	Macrophage_Lung	Macrophage cells with lung tissue origins	MIDN	-0.204931
abT	alpha beta T cells	ZNF516	-0.246461708	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	SPOCK2	-0.05739	Macrophage_Lung	Macrophage cells with lung tissue origins	MISP3	0.0084275
B_mature	mature B cells	(Intercept)	-1.549992694	Macrophage_clus7	Macrophage cells, k-means defined cluster 7	USP53	-0.04631	Macrophage_Lung	Macrophage cells with lung tissue origins	NSMAF	-0.178247
B_mature	mature B cells	ATP11A	-0.031583511	Mast_cell	Mast cells	(Intercept)	-6.320001	Macrophage_Lung	Macrophage cells with lung tissue origins	SLC9A4	0.035116
B_mature	mature B cells	CACNA1I	0.063664894	Mast_cell	Mast cells	SMPX	0.115906	Macrophage_Lung	Macrophage cells with lung tissue origins	TBX4	0.5009861
B_mature	mature B cells	KLHL14	0.535385558	Mast_cell	Mast cells	STK32B	0.3220007	Macrophage_Other	Macrophage cells with other tissue origins	(Intercept)	-10.86262
B_mature	mature B cells	LCP2	-0.50433392	Mast_cell	Mast cells	TPSAB1	0.0001682	Macrophage_Other	Macrophage cells with other tissue origins	A4GALT	0.3428367
CD8.T.act	CD8+ activated T cells	(Intercept)	-6.64893008	Mast_cell	Mast cells	TPSB2	1.60E-15	Macrophage_Other	Macrophage cells with other tissue origins	AAR2	0.1886536
CD8.T.act	CD8+ activated T cells	GZMM	0.080056183	Mast_cell	Mast cells	TPSG1	0.7737122	Macrophage_Other	Macrophage cells with other tissue origins	AKT3	-0.052303
CD8.T.act	CD8+ activated T cells	LRRC75B	0.362673397	Microglia	Microglial cells	(Intercept)	-3.274518	Macrophage_Other	Macrophage cells with other tissue origins	ASGR2	0.1333548
CD8.T.act	CD8+ activated T cells	MMP16	0.086408591	Microglia	Microglial cells	ATP13A5	0.0254463	Macrophage_Other	Macrophage cells with other tissue origins	C3orf62	-0.068357
CD8.T.act	CD8+ activated T cells	NCMAP	-0.045303327	Microglia	Microglial cells	COX14	-0.155755	Macrophage_Other	Macrophage cells with other tissue origins	CFD	0.2517181

CD8.T.act	CD8+ activated T cells	OSGIN1	-0.096222092	Microglia	Microglial cells	COX6B1	-0.487811	Macrophage_Other	Macrophage cells with other tissue origins	DLST	0.583357
CD8.T.act	CD8+ activated T cells	TRAV23DV6	0.712614542	Microglia	Microglial cells	CSMD3	0.3769117	Macrophage_Other	Macrophage cells with other tissue origins	EPOR	0.1387225
CD8.T.act	CD8+ activated T cells	WFIKKN2	0.335981436	Microglia	Microglial cells	MEIG1	0.0293387	Macrophage_Other	Macrophage cells with other tissue origins	FAM83G	-0.01287
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	(Intercept)	-8.123768812	Microglia	Microglial cells	PFN1	-0.152983	Macrophage_Other	Macrophage cells with other tissue origins	GPC4	0.0370189
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	ACTR1B	0.158306819	Microglia	Microglial cells	SLCO1C1	0.0746896	Macrophage_Other	Macrophage cells with other tissue origins	GSK3A	-0.198529
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	CADM3	0.023449502	Microglia	Microglial cells	TMX4	0.5382676	Macrophage_Other	Macrophage cells with other tissue origins	IGF2BP1	0.2902343
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	CCDC170	0.126059806	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	(Intercept)	-12.3884	Macrophage_Other	Macrophage cells with other tissue origins	IGF2BP3	0.003376
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	DKK2	0.285146848	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ACE	0.4953719	Macrophage_Other	Macrophage cells with other tissue origins	IL4I1	-0.027645
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	MMP12	0.033976559	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ADAM32	-0.130983	Macrophage_Other	Macrophage cells with other tissue origins	LDB3	-0.046662
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	NCCRP1	0.447996595	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ADAMTS4	-0.118824	Macrophage_Other	Macrophage cells with other tissue origins	LIMCH1	-0.027317
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	PNPO	0.110169671	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ALB	0.1326397	Macrophage_Other	Macrophage cells with other tissue origins	LRAT	-0.250784
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	PPP1R14A	0.252866799	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	C3orf20	-0.043665	Macrophage_Other	Macrophage cells with other tissue origins	MMP13	0.1846006
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	RADIL	0.062270484	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	CCDC68	0.1930406	Macrophage_Other	Macrophage cells with other tissue origins	NEXN	-0.098988
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	STK32C	0.019624646	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	CTNNA3	-0.081262	Macrophage_Other	Macrophage cells with other tissue origins	P2RX6	0.0591444
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	SUCNR1	0.407838462	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	CXCL11	0.0169017	Macrophage_Other	Macrophage cells with other tissue origins	PBXIP1	-0.074238
Dendritic_clus1	Dendritic cells, k-means defined cluster 1	TRAPPC5	0.008898636	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	CXCL9	0.0945416	Macrophage_Other	Macrophage cells with other tissue origins	PLN	-0.095633

Dendritic_clus 1	Dendritic cells, k-means defined cluster 1	VRK1	0.386902817	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	CYP1A1	0.0094036	Macrophage_Other	Macrophage cells with other tissue origins	PPP1R3C	-0.094268
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	(Intercept)	-6.722646121	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	DNAH6	-0.117278	Macrophage_Other	Macrophage cells with other tissue origins	PRKCE	-0.062716
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	CLTRN	0.568477717	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ENPP6	-0.018847	Macrophage_Other	Macrophage cells with other tissue origins	SEC14L4	-0.06227
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	DDX58	-0.03843886	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	ETHE1	0.2915961	Macrophage_Other	Macrophage cells with other tissue origins	SLC13A3	0.0941934
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	GRAMD2A	0.153602144	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	FCN1	0.0807263	Macrophage_Other	Macrophage cells with other tissue origins	SMOC2	0.0588569
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	PPT1	0.459595114	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	FLRT3	-0.073566	Macrophage_Other	Macrophage cells with other tissue origins	TAF11	0.045049
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	WLS	-0.119007461	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	FUT9	-0.204966	Macrophage_Other	Macrophage cells with other tissue origins	TBX4	-0.520128
Dendritic_clus 2	Dendritic cells, k-means defined cluster 2	XCR1	0.050767932	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	GDF15	0.0934752	Macrophage_Other	Macrophage cells with other tissue origins	TEAD2	-0.30886
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	(Intercept)	-13.3434289	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	GDF3	0.189272	Macrophage_Other	Macrophage cells with other tissue origins	TMOD1	0.1696014
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	CEBPZ	-0.043224663	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	GLP1R	0.3059683	Macrophage_Other	Macrophage cells with other tissue origins	TNNC1	-0.162403
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	DAO	0.12683647	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	GPNMB	0.1573053	Macrophage_Other	Macrophage cells with other tissue origins	TSPAN10	0.1474647
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	DCAF12	-0.121365297	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	KLK1	0.0809401	Macrophage_Other	Macrophage cells with other tissue origins	WDR36	0.0373679
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	EHMT1	0.213071073	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	LNX1	-0.080215	Macrophage_Other	Macrophage cells with other tissue origins	XRCC1	0.2726984
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	EIF4G3	-0.241703538	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	MROH2A	-0.013603	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	(Intercept)	-7.886531
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	MMP7	0.390350102	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	MYRF	-0.025713	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	BCAM	0.0034573

Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	OPRD1	0.119991091	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	NR0B2	0.0356621	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	FABP7	0.0139429
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	POLR3C	1.084677505	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	PTPRB	0.3180536	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	FAM20A	0.1139873
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	RGS6	0.188014525	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	RNF222	-0.015217	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	FAM78B	0.2362067
Dendritic_clus 3	Dendritic cells, k-means defined cluster 3	TBC1D17	0.289201175	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	SDK2	-0.378768	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	GLB1	0.0496994
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	(Intercept)	-13.5669761	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	SLC1A2	-0.065051	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	HAL	0.1725152
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	BTBD1	-0.702940517	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	SYNGR1	0.0108365	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	KDM6B	-0.022042
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	ELANE	0.311312019	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	TMEM117	-0.080936	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	LIPN	0.0626554
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	GALM	-0.008124744	Monocyte_clus1	Monocyte cells, k-means defined cluster 1	VIPAS39	0.4075701	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	MST1R	0.1016218
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	GTDC1	-0.283430504	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	(Intercept)	-10.00118	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	PADI4	0.0385276
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	KAT7	0.070669481	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	CAPRIN2	-0.120379	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	PYCARD	0.2990131
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	MPO	0.065416945	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	CENPE	-0.112678	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	RARB	0.5058355
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	NKX2-3	0.004093534	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	CXCL11	0.0059509	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	RNF141	0.0399126
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	PAQR5	0.063290853	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	GPLD1	0.1435982	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	SPATA13	-0.18623
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	PLA2G4D	0.553801138	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	HIF1A	0.4876146	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	VAMP4	0.1420015
Dendritic_clus 4	Dendritic cells, k-means defined cluster 4	PNCK	0.334293496	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	HLA-DRA	-0.006791	Macrophage_Peritoneal_Cavity	Macrophage cells with peritoneal cavity tissue origins	VSIG8	0.1705707

Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	RAB33B	0.370419827	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	HOPX	0.0075312	Monocyte_all	Monocyte cells	(Intercept)	-3.1518
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	RGP1	0.444839022	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	IMMP2L	-0.016049	Monocyte_all	Monocyte cells	ACE	0.187378
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	RNF11	-0.263831387	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	JADE2	-0.091665	Monocyte_all	Monocyte cells	ALDH3B2	-0.040236
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	RNF220	0.006810057	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	KYAT1	-0.258265	Monocyte_all	Monocyte cells	ARHGEF37	0.2068529
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	RNU4-2	0.063610658	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	LSM11	-0.026337	Monocyte_all	Monocyte cells	CCNO	-0.082706
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	SLC34A1	0.013380526	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	MBLAC2	-0.190036	Monocyte_all	Monocyte cells	CENPE	-0.118123
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	TEX2	0.036354183	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	MPIG6B	0.0296941	Monocyte_all	Monocyte cells	CEP89	-0.026038
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	THEM6	0.063757031	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	MRNIP	-0.076447	Monocyte_all	Monocyte cells	CYP4B1	0.0017585
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	TRAPPC5	1.033001367	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	PCID2	0.426335	Monocyte_all	Monocyte cells	DAXX	0.2480184
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	TRIM58	0.031600281	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	PTCH1	-0.214745	Monocyte_all	Monocyte cells	DCBLD2	-0.059914
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	UPB1	0.205840822	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	RAD9B	-0.229406	Monocyte_all	Monocyte cells	GABBR1	-0.291848
Dendritic_clus_4	Dendritic cells, k-means defined cluster 4	ZDHHC19	0.471118953	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	REST	0.4973285	Monocyte_all	Monocyte cells	GPLD1	0.1297842
gdT	gamma-delta T cells	(Intercept)	-6.017483799	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	RHOV	0.0636676	Monocyte_all	Monocyte cells	JADE1	-0.277935
gdT	gamma-delta T cells	CCR10	0.097500198	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	SH2D6	0.3383157	Monocyte_all	Monocyte cells	KIF18A	-0.06814
gdT	gamma-delta T cells	DAPL1	0.078407795	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	TM4SF19	0.113478	Monocyte_all	Monocyte cells	LETM2	-0.123993
gdT	gamma-delta T cells	FAM124B	0.122009728	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	TM4SF19-	1.71E-17	Monocyte_all	Monocyte cells	MARVELD1	-0.065281

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gdT	gamma-delta T cells	GGT1	0.0534037	Monocyte_clus2	Monocyte cells, k-means defined cluster 2	ULK1	-0.000917	Monocyte_all	Monocyte cells	MCF2L	0.1285281
gdT	gamma-delta T cells	SOX13	0.460115544	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	(Intercept)	-4.785432	Monocyte_all	Monocyte cells	MSRB2	-0.048449
gdT	gamma-delta T cells	TRDC	0.38370397	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	CCDC192	0.3610516	Monocyte_all	Monocyte cells	NECAP1	0.0826144
ILC	Innate lymphoid cells	(Intercept)	-3.616471171	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	SCNN1A	0.1586076	Monocyte_all	Monocyte cells	OTUD7B	-0.071734
ILC	Innate lymphoid cells	CRYGN	0.130466746	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	SCNN1G	0.0844571	Monocyte_all	Monocyte cells	PLAC8	0.0420314
ILC	Innate lymphoid cells	KLHL30	1.46E-05	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	TGM3	0.1254089	Monocyte_all	Monocyte cells	PLEKHF2	0.0183138
ILC	Innate lymphoid cells	KLRG1	0.025191909	Monocyte_clus3	Monocyte cells, k-means defined cluster 3	TMEM121B	0.6782325	Monocyte_all	Monocyte cells	PPP1R3G	-0.112416
ILC	Innate lymphoid cells	MATK	-0.180422579	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	(Intercept)	-3.234572	Monocyte_all	Monocyte cells	RSPO1	0.3097449
ILC	Innate lymphoid cells	NCR1	0.375227391	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	C1GALT1C1	0.2737209	Monocyte_all	Monocyte cells	SFTPB	0.1710195
ILC	Innate lymphoid cells	NMUR1	0.448198899	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	CD9	-0.051805	Monocyte_all	Monocyte cells	SH2D6	0.2448665
ILC	Innate lymphoid cells	PHACTR3	0.174855253	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	DCST2	0.01848	Monocyte_all	Monocyte cells	SYNE2	-0.018358
ILC	Innate lymphoid cells	RASGEF1C	0.003713342	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	DIABLO	-0.370062	Monocyte_all	Monocyte cells	SYT8	-0.09532
ILC	Innate lymphoid cells	RET	0.132813605	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	GOT1	-0.213832	Monocyte_all	Monocyte cells	TBC1D19	-0.06701
ILC	Innate lymphoid cells	SCARB1	-0.07105525	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	JADE2	-0.034674	Monocyte_all	Monocyte cells	TONSL	-0.006234
ILC	Innate lymphoid cells	SPRY2	0.013616034	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	MGAT4A	-0.218986	Monocyte_all	Monocyte cells	VSIG8	-0.079298
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	(Intercept)	-7.091174516	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	RBKS	0.5059444	Monocyte_all	Monocyte cells	ZFYVE9	0.143403
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	ADAMDEC1	0.082406686	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	RSPO1	0.5938048	Monocyte_all	Monocyte cells	ZNF76	-0.137201
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	ANKDD1A	-0.120502141	Monocyte_clus4	Monocyte cells, k-means defined cluster 4	TSTD1	0.0312869	B_all	B cells	(Intercept)	-1.327731
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	B3GNT7	0.02882706	stem	stem cells	(Intercept)	-5.451469	B_all	B cells	BFSP2	0.1144329

Macrophage_clus1	Macrophage cells, k-means defined cluster 1	FAM83F	0.096395206	stem	stem cells	DACH1	0.0523615	B_all	B cells	FYB1	-0.043922
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	HAMP	-0.03965109	stem	stem cells	HOXA10	0.0228399	B_all	B cells	IGHV1-24	0.6209573
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	IGF2BP3	0.056557041	stem	stem cells	MAP7D2	0.4619375	B_all	B cells	IGHV1-46	9.94E-15
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	KCNJ10	0.01181564	stem	stem cells	MPL	0.2202485	B_all	B cells	IGHV1-69	4.58E-16
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	LGI4	0.036759845	stem	stem cells	NKX2-3	0.734782	B_all	B cells	IGHV1OR15-9	0.1739779
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	MATN3	0.026126966	stem	stem cells	SAMD12	0.0350193	B_all	B cells	IGHV2-26	0.0594361
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	MMP12	0.08377652	stroma	stromal cells	(Intercept)	-4.394228	B_all	B cells	IGHV2-5	3.64E-15
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	MMP13	0.268521879	stroma	stromal cells	IGFBP5	0.2713573	B_all	B cells	IGHV2-70	9.80E-17
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	PARP9	0.065091506	stroma	stromal cells	MSX1	0.2815415	B_all	B cells	IGHV2-70D	3.92E-17
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	RAG1	0.046479459	stroma	stromal cells	PRSS23	0.0936651	B_all	B cells	IGHV3-15	0.0022022
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	SLC13A3	0.046205156	stroma	stromal cells	RGS4	0.1496425	B_all	B cells	KCNG1	0.0696491
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	SLC6A1	-0.006575066	stroma	stromal cells	STC1	0.1310073	B_all	B cells	MZB1	0.0639528
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	SPON1	0.087465459	stroma	stromal cells	TNC	0.0550913	B_all	B cells	PAX5	0.0165548
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	TCF21	0.259197858	stroma	stromal cells	UBD	0.1262248	B_all	B cells	PPM1H	-0.487917
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	TMEM117	-0.032205423	Dendritic_cell_all	Dendritic cells	(Intercept)	-5.912319	B_all	B cells	PPP1R36	0.0671497

Macrophage_clus1	Macrophage cells, k-means defined cluster 1	TRIM55	0.268894639	Dendritic_cell_all	Dendritic cells	ADAM11	0.1002379	B_all	B cells	VPREB3	0.270114
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	TSPAN10	0.135826007	Dendritic_cell_all	Dendritic cells	AP1S3	0.0214533	Macrophage_all	Macrophage cells	(Intercept)	0.7265421
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	VIPAS39	0.291509288	Dendritic_cell_all	Dendritic cells	BCL2L14	0.0092591	Macrophage_all	Macrophage cells	ACY3	0.0151788
Macrophage_clus1	Macrophage cells, k-means defined cluster 1	ZFYVE28	0.096370959	Dendritic_cell_all	Dendritic cells	BLOC1S2	0.6153238	Macrophage_all	Macrophage cells	AGMO	0.0121083
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	(Intercept)	-4.020385943	Dendritic_cell_all	Dendritic cells	CACNG8	0.1962639	Macrophage_all	Macrophage cells	ANKRD12	-0.186162
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	C6	0.248733891	Dendritic_cell_all	Dendritic cells	CD84	-0.056769	Macrophage_all	Macrophage cells	ASB4	0.1293867
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	DYSF	0.215674654	Dendritic_cell_all	Dendritic cells	CNTRL	0.0341237	Macrophage_all	Macrophage cells	ATP13A5	-0.008178
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	FGG	0.095031229	Dendritic_cell_all	Dendritic cells	COL23A1	0.0634118	Macrophage_all	Macrophage cells	B3GLCT	0.016268
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	PCOLCE2	0.055627283	Dendritic_cell_all	Dendritic cells	DDX58	-0.006258	Macrophage_all	Macrophage cells	C2CD3	-0.003533
Macrophage_clus2	Macrophage cells, k-means defined cluster 2	STAB2	0.030343236	Dendritic_cell_all	Dendritic cells	FFAR4	0.0680295	Macrophage_all	Macrophage cells	CANX	0.040146
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	(Intercept)	-8.230602674	Dendritic_cell_all	Dendritic cells	FLT3	0.0678801	Macrophage_all	Macrophage cells	CASC3	-0.007099
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	HES2	0.577907806	Dendritic_cell_all	Dendritic cells	GPR4	0.0187906	Macrophage_all	Macrophage cells	CCL24	0.0082989
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	HIBCH	-0.061966381	Dendritic_cell_all	Dendritic cells	LPAR3	0.0846475	Macrophage_all	Macrophage cells	CD2BP2	-0.150476
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	HLA-DRA	0.054458451	Dendritic_cell_all	Dendritic cells	MTMR14	0.036754	Macrophage_all	Macrophage cells	CPE	-0.004293
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	KLK13	0.052526618	Dendritic_cell_all	Dendritic cells	MYCL	0.0313354	Macrophage_all	Macrophage cells	CXCL14	0.0657919

Macrophage_clus3	Macrophage cells, k-means defined cluster 3	LGI3	0.550751383	Dendritic_cell_all	Dendritic cells	NCCRP1	0.069873	Macrophage_all	Macrophage cells	DENND3	-0.008955
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	RBPJL	0.676278283	Dendritic_cell_all	Dendritic cells	NME9	0.0015251	Macrophage_all	Macrophage cells	EFEMP2	0.1616696
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	RTBDN	0.020583144	Dendritic_cell_all	Dendritic cells	POLG	-0.122899	Macrophage_all	Macrophage cells	ELF4	-0.008196
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	SAP18	0.474280619	Dendritic_cell_all	Dendritic cells	SH3BP5	-0.081743	Macrophage_all	Macrophage cells	EME2	-0.161664
Macrophage_clus3	Macrophage cells, k-means defined cluster 3	TCOF1	0.335241139	Dendritic_cell_all	Dendritic cells	ZBTB46	0.0753025	Macrophage_all	Macrophage cells	GBGT1	0.2021341
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	(Intercept)	-3.729871533	Dendritic_cell_all	Dendritic cells	ZMIZ2	0.1389079	Macrophage_all	Macrophage cells	GPATCH11	-0.050541
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	CALHM2	-0.038894611	granulocyte	Granulocytes	(Intercept)	-1.573921	Macrophage_all	Macrophage cells	GPLD1	-0.016197
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	CTSK	0.15724825	granulocyte	Granulocytes	BPNT1	-0.398936	Macrophage_all	Macrophage cells	HSH2D	-0.036164
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	DUSP13	0.377946852	granulocyte	Granulocytes	CKLF	0.0768094	Macrophage_all	Macrophage cells	IL1A	0.0584859
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	RCSD1	-0.0752708	granulocyte	Granulocytes	CLCN3	-0.005616	Macrophage_all	Macrophage cells	MGMT	0.1032007
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	TRIM29	0.024329186	granulocyte	Granulocytes	CLPB	-0.150694	Macrophage_all	Macrophage cells	MRC1	0.1710779
Macrophage_clus4	Macrophage cells, k-means defined cluster 4	ZFAND2A	0.30151853	granulocyte	Granulocytes	EDNRA	0.1639499	Macrophage_all	Macrophage cells	MYO1H	-0.071332
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	(Intercept)	-7.12929125	granulocyte	Granulocytes	MS4A2	0.2927978	Macrophage_all	Macrophage cells	MYO7A	0.0757502
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	CALML4	0.103286223	granulocyte	Granulocytes	NCAM1	0.1325591	Macrophage_all	Macrophage cells	NEURL1	0.0897319
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	CLRN3	0.017322042	granulocyte	Granulocytes	NLRP12	0.390913	Macrophage_all	Macrophage cells	NXPE3	-0.051996

Macrophage_clus5	Macrophage cells, k-means defined cluster 5	DTX3	-0.140238486	granulocyte	Granulocytes	SLC25A4	-0.09173	Macrophage_all	Macrophage cells	PCP4L1	-0.046003
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	GATA6	0.39415529	granulocyte	Granulocytes	SLC41A1	-0.053435	Macrophage_all	Macrophage cells	PKP3	-0.003309
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	ICAM2	0.050052326	granulocyte	Granulocytes	STK32B	0.2356176	Macrophage_all	Macrophage cells	PLAC8	-0.040104
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	PFKL	0.023916193	granulocyte	Granulocytes	TMEM40	0.0298787	Macrophage_all	Macrophage cells	PPP1R3G	0.1983249
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	PRG4	0.110299091	granulocyte	Granulocytes	ZNF146	-0.153386	Macrophage_all	Macrophage cells	RHOC	0.057847
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	PYCARD	0.287196787	Macrophage_Brain	Macrophage cells with brain tissue origins	(Intercept)	-4.106222	Macrophage_all	Macrophage cells	RSPO1	-0.064499
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	RP1	0.173075061	Macrophage_Brain	Macrophage cells with brain tissue origins	AKAP3	0.0374379	Macrophage_all	Macrophage cells	SERPINB6	0.1218214
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	SELP	0.055773841	Macrophage_Brain	Macrophage cells with brain tissue origins	ARR3	-0.017346	Macrophage_all	Macrophage cells	SH2D3C	-0.16929
Macrophage_clus5	Macrophage cells, k-means defined cluster 5	WNT2	0.100552962	Macrophage_Brain	Macrophage cells with brain tissue origins	ASB16	-0.009873	Macrophage_all	Macrophage cells	SHLD2	-0.141058
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	(Intercept)	-4.132570306	Macrophage_Brain	Macrophage cells with brain tissue origins	CLGN	0.0509409	Macrophage_all	Macrophage cells	SLCO1C1	-0.095745
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	ADAMDEC1	-0.008257374	Macrophage_Brain	Macrophage cells with brain tissue origins	EBF4	-0.021489	Macrophage_all	Macrophage cells	SMARCD3	-0.00475
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	ANAPC7	0.105478953	Macrophage_Brain	Macrophage cells with brain tissue origins	EFCAB6	-0.188585	Macrophage_all	Macrophage cells	SNRPC	-0.03814
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	AP1B1	0.232559156	Macrophage_Brain	Macrophage cells with brain tissue origins	ENAM	-0.068888	Macrophage_all	Macrophage cells	SPOCK2	-0.036981
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	CD207	-0.002113765	Macrophage_Brain	Macrophage cells with brain tissue origins	HPCAL4	0.1597102	Macrophage_all	Macrophage cells	TRIM56	-0.063329
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	CDKL4	-0.056586152	Macrophage_Brain	Macrophage cells with brain tissue origins	HSPB3	1.3420763	Macrophage_all	Macrophage cells	VRK3	-0.02568

Macrophage_clus6	Macrophage cells, k-means defined cluster 6	CLCF1	-0.044286212	Macrophage_Brain	Macrophage cells with brain tissue origins	KLF2	-0.236661	Macrophage_all	Macrophage cells	VTN	-0.090261
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	DENND3	-0.106884529	Macrophage_Brain	Macrophage cells with brain tissue origins	MEIG1	-0.274868	Macrophage_all	Macrophage cells	VWA3B	-0.018121
Macrophage_clus6	Macrophage cells, k-means defined cluster 6	DOT1L	-0.044799992	Macrophage_Brain	Macrophage cells with brain tissue origins	QRFPR	0.3079325	Macrophage_all	Macrophage cells	ZNF217	-0.035176

[0381] Each tumor's gene expression data was processed identically. Experiment data was converted to a DGE list using the R (version 4.1.1) function SE2DGEList in the edgeR package(Robinson, McCarthy et al. 2010). Duplicate genes were reduced to a single gene by selecting the gene with the maximum standard deviation across all samples in the data set. Mouse gene names were converted to human orthologs using biomaRt(Durinck, Spellman et al. 2009). When there was gene duplication in orthologs, the gene with greatest homology with a human ortholog was retained. HUGO Gene Nomenclature Committee (HGNC) names for each gene were added using the biomarRt package. Genes without a HGNC designation were removed from the analysis. Using TMM normalization in the EdgeR package, normalization factors were calculated, applied, and log2 transformed counts per million (cpm) were determined for each gene for each sample. The distribution of cpm and the standard deviation of genes across samples was plotted, and cutoffs determined to remove very low expressing genes. Samples were then renormalized using TMM after these genes were removed.

[0382] *Creation of working set of immune markers.*

[0383] Genes that are differentially expressed in specific immune cell types were nominated from a variety of published sources. To validate the given association of the genes with immune cell types, RNASeq data from defined mouse immune cell populations from the ImmGen project GSE109125 (Yoshida, Lareau et al. 2019) and GSE122108 (ImmGen 2016) and defined human immune cell populations GSE22886 (Abbas, Baldwin et al. 2005) were used. As definitions of immune cell type differed between studies, the cell types were simplified to B lymphoid, non-B lymphoid, and myeloid types. A Student T-test was used to determine if the expression in the corresponding category of defined cells was greater than expected by chance. Genes with a positive T score and a p value less than 0.05 in either the mouse or human RNASeq data sets were retained for further use, resulting in 680 immune markers. To keep the number of markers for each cell type balanced as some cell types had a markedly greater number of nominated markers than others, the genes were ranked by p value and a maximum of 24 markers (mean of number of genes associated with each specific cell type, e.g. 'M2D macrophage') were retained. If the number of genes within a particular annotation was less than 12 (1st quartile of genes associated with each

cell type), then no attempt was made to model that cell type. Published sources for certain genes used for model building in the present disclosure are presented in Table 41B.

[0384] Table 41B: Published sources from which candidate immune genes were used for model building,

Source	Link or publication information
CellMarker	Congxue Hu, Tengyue Li, Yingqi Xu, Xinxin Zhang, Feng Li, Jing Bai, Jing Chen, Wenqi Jiang, Kaiyue Yang, Qi Ou, Xia Li, Peng Wang, Yunpeng Zhang, CellMarker 2.0: an updated database of manually curated cell markers in human/mouse and web tools based on scRNA-seq data,ï¿½Nucleic Acids Research, Volume 51, Issue D1, 6 January 2023, Pages D870ï¿½D876,ï¿½ https://protect-us.mimecast.com/s/g1s7CPN6MGtZgvApC6p2C_?domain=doi.org
Pangluo DB	Oscar Franzï¿½n, Li-Ming Gan, Johan L M Bjï¿½rkegren,ï¿½PanglaoDB: a web server for exploration of mouse and human single-cell RNA sequencing data,ï¿½Database, Volume 2019, 2019, baz046,ï¿½doi:10.1093/database/baz046
BIORAD	https://protect-us.mimecast.com/s/xu_iCQWANXC9VB40UA9brP?domain=bio-rad-antibodies.com
Macrophage Polarization - Mini-review | Bio-Rad (https://protect-us.mimecast.com/s/KOY4CR68MXCQYnP2fQhJ0T?domain=bio-rad-antibodies.com)	bio-rad-antibodies.com
Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. J Leukoc Biol. 2019;106(2):345-358.	Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. J Leukoc Biol. 2019;106(2):345-358.
Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)	Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)

Trombetta AC, Soldano S, Contini P, et al. A circulating cell population showing both M1 and M2 monocyte/macrophage surface markers characterizes systemic sclerosis patients with lung involvement. Respir Res. 2018;19(1):186.	Trombetta AC, Soldano S, Contini P, et al. A circulating cell population showing both M1 and M2 monocyte/macrophage surface markers characterizes systemic sclerosis patients with lung involvement. Respir Res. 2018;19(1):186.
Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)	Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)
Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)	Jablonski KA, Amici SA, Webb LM, et al. Novel Markers to Delineate Murine M1 and M2 Macrophages. PLoS One. 2015;10(12)
Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. J Leukoc Biol. 2019;106(2):345-358.	Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. J Leukoc Biol. 2019;106(2):345-358.
J Immunol. 2016 March 15; 196(6): 2847i¿½2859.	Poczobutt JM, De S, Yadav VK, Nguyen TT, Li H, Sippel TR, Weiser-Evans MC, Nemenoff RA. Expression Profiling of Macrophages Reveals Multiple Populations with Distinct Biological Roles in an Immunocompetent Orthotopic Model of Lung Cancer. J Immunol. 2016 Mar 15;196(6):2847-59. doi: 10.4049/jimmunol.1502364. Epub 2016 Feb 12. PMID: 26873985; PMCID: PMC4779748.
Macrophage Polarization - Mini-review | Bio-Rad (https://protect-us.mimecast.com/s/KOY4CR68MXCQYnP2fQhJ0T?domain=bio-rad-antibodies.com)	Macrophage Polarization - Mini-review | Bio-Rad (https://protect-us.mimecast.com/s/KOY4CR68MXCQYnP2fQhJ0T?domain=bio-rad-antibodies.com)
Tumor Associated Neutrophils. Their Role in Tumorigenesis, Metastasis, Prognosis and Therapy (https://protect-us.mimecast.com/s/IfjiCVOJ5WiXB0jGSEuhiF?domain=nih.gov)	Masucci MT, Minopoli M and Carriero MV (2019) Tumor Associated Neutrophils. Their Role in Tumorigenesis, Metastasis, Prognosis and Therapy. Front. Oncol. 9:1146. doi: 10.3389/fonc.2019.01146

Wang X, Qiu L, Li Z, Wang XY, Yi H. Understanding the Multifaceted Role of Neutrophils in Cancer and Autoimmune Diseases. Front Immunol. 2018;9:2456.	Wang X, Qiu L, Li Z, Wang XY, Yi H. Understanding the Multifaceted Role of Neutrophils in Cancer and Autoimmune Diseases. Front Immunol. 2018;9:2456.
Morgan A. Giese, Laurel E. Hind, Anna Huttenlocher; Neutrophil plasticity in the tumor microenvironment. Blood 2019; 133 (20): 2159ï¿½2167.	Morgan A. Giese, Laurel E. Hind, Anna Huttenlocher; Neutrophil plasticity in the tumor microenvironment. Blood 2019; 133 (20): 2159ï¿½2167.
BioCompare	https://protect-us.mimecast.com/s/wb7KCW6Ww1Cx3zwJIOCL_r?domain=biocompare.com

[0385] *Creation of network modeling of shared immune genes*

[0386] Gene expression data for the training sets of solid tumors in the TCGA20 (lung squamous cell, lung adenocarcinoma, breast, ovarian, kidney clear cell, head and neck, prostate, colon, bladder, pancreas, kidney papillary, rectal, kidney chromophobe, esophageal, stomach cancers) were each individually scaled. The RNASeq exression data sets were limited to the immune markers as described (N=758). These scaled data sets were then fuzzy clustered using fclust (Ferraro, Giordani et al. 2019), with k=15. Clusters of genes identified by this process were limited to genes whose expression was three standard deviations above the mean for all genes. Clusters were only selected for further use if they contained at least five genes. These selected clusters for all fifteen tumors were combined and then used to create a network, and clusters of genes were defined by the cluster_louvain function in igraph (Blondel, Guillaume et al. 2008). Each set of genes defined in these network models were named based on annotation of the contributing genes in terms of their curated association with immune cell types Weights for each gene in a network signature were derived using the mean of all fuzzy clustering gene scores. Samples are scored with these models via a determining of the weighted mean score for each sample using the genes of each network signature set. Genes and coefficients are presented in Table 42.

[0387] Table 42: Immune gene network signatures.

Model name	Simplified model name	Gene name	Gene weight	Model name	Simplified model name	Gene name	Gene weight	Model name	Simplified model name	Gene name	Gene weight
NC_Tc_PC_Tr_B	non-B Lymphoid 1	PTPRC	0.917325418	Tgd_T_Tm	non-B Lymphoid 3	CTLA4	0.738854239	Mo_Baso_M_M2_Mast_MK	Myeloid 3	DYSF	0.613825168
NC_Tc_PC_Tr_B	non-B Lymphoid 1	IKZF1	0.854261396	Tgd_T_Tm	non-B Lymphoid 3	TIGIT	0.889416557	Mo_Baso_M_M2_Mast_MK	Myeloid 3	ACE	0.437208174
NC_Tc_PC_Tr_B	non-B Lymphoid 1	IRF8	0.83718805	Tgd_T_Tm	non-B Lymphoid 3	CCL5	0.902009794	Mo_Baso_M_M2_Mast_MK	Myeloid 3	S1PR1	0.859626705
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CCR2	0.626339138	Tgd_T_Tm	non-B Lymphoid 3	TBX21	0.783005531	Mo_Baso_M_M2_Mast_MK	Myeloid 3	VWF	0.669753942
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CD40LG	0.700167609	Tgd_T_Tm	non-B Lymphoid 3	CD7	0.806232456	Mo_Baso_M_M2_Mast_MK	Myeloid 3	ZBTB16	0.651179019
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CSF2RB	0.653807747	Tgd_T_Tm	non-B Lymphoid 3	CCL4	0.848241653	Mo_Baso_M_M2_Mast_MK	Myeloid 3	CFP	0.44063352
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CCR4	0.691980433	Tgd_T_Tm	non-B Lymphoid 3	TRDC	0.670793137	Mo_Baso_M_M2_Mast_MK	Myeloid 3	FGFBP2	0.638039851
NC_Tc_PC_Tr_B	non-B Lymphoid 1	PTGDS	0.577573099	Tgd_T_Tm	non-B Lymphoid 3	FASLG	0.948719515	Mo_Baso_M_M2_Mast_MK	Myeloid 3	CD36	0.717409509
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CD37	0.804972636	D_N_M	Myeloid 1	CD180	0.818123022	Mo_Baso_M_M2_Mast_MK	Myeloid 3	IGF1	0.691052422
NC_Tc_PC_Tr_B	non-B Lymphoid 1	IL16	0.780911078	D_N_M	Myeloid 1	CD14	0.862053164	Mo_Baso_M_M2_Mast_MK	Myeloid 3	DAB2	0.557080727
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CLEC10A	0.579434053	D_N_M	Myeloid 1	FCGR1A	0.788506002	Mo_Baso_M_M2_Mast_MK	Myeloid 3	TLR4	0.626384948
NC_Tc_PC_Tr_B	non-B Lymphoid 1	IL7R	0.691393804	D_N_M	Myeloid 1	AIF1	0.878369526	Mo_Baso_M_M2_Mast_MK	Myeloid 3	LRP1	0.604761842
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CD69	0.50293393	D_N_M	Myeloid 1	TLR8	0.855379385	Mo_Baso_M_M2_Mast_MK	Myeloid 3	VCAM1	0.595818898
NC_Tc_PC_Tr_B	non-B Lymphoid 1	SELL	0.600787357	D_N_M	Myeloid 1	FCGR3A	0.903577469	Mo_Baso_M_M2_Mast_MK	Myeloid 3	FN1	0.621558355
NC_Tc_PC_Tr_B	non-B Lymphoid 1	CD28	0.686122434	D_N_M	Myeloid 1	HAVCR2	0.95209179	Mo_Baso_M_M2_Mast_MK	Myeloid 3	NT5E	0.512603299
NC_Tc_PC_Tr_B	non-B Lymphoid 1	ICOS	0.664203652	D_N_M	Myeloid 1	MNDA	0.877753077	Mo_Baso_M_M2_Mast_MK	Myeloid 3	TNFSF4	0.648997326
NC_Tc_PC_Tr_B	non-B Lymphoid 1	PTPN22	0.61607136	D_N_M	Myeloid 1	CMKLR1	0.856603997	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	IL4R	0.566193934
NC_Tc_PC_Tr_B	non-B Lymphoid 1	BCL11B	0.609119483	D_N_M	Myeloid 1	CSF1R	0.888130199	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	MAFG	0.560799162
NC_Tc_PC_Tr_B	non-B Lymphoid 1	RGS18	0.370643898	D_N_M	Myeloid 1	SIGLEC1	0.85613325	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	TRAF4	0.562977321

NC_Tc_PC_Tr_B	non-B Lymphoid 1	FCGR2C	0.256895259	D_N_M	Myeloid 1	C3AR1	0.948899775	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	KIF5B	0.679717963
NC_Tc_PC_Tr_B	non-B Lymphoid 1	TMEM156	0.270859513	D_N_M	Myeloid 1	CCR1	0.860443369	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	STAT3	0.785791656
B_Bmem	B cells	BLK	0.890181803	D_N_M	Myeloid 1	MSR1	0.885921785	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	TET2	0.793797205
B_Bmem	B cells	TNFRSF13B	0.876186917	D_N_M	Myeloid 1	TYROBP	0.896458165	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	BCL7A	0.650442077
B_Bmem	B cells	CD19	0.910624235	D_N_M	Myeloid 1	FCGR2A	0.82660907	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	SUPT3H	0.475839276
B_Bmem	B cells	CD79B	0.897000018	D_N_M	Myeloid 1	CD163	0.908990209	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	EPOR	0.716431271
B_Bmem	B cells	POU2AF1	0.920626349	D_N_M	Myeloid 1	MS4A4A	0.954017257	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	PPARG	0.620783906
B_Bmem	B cells	IGLC3	0.952422944	D_N_M	Myeloid 1	VSIG4	0.864592262	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	ITGA2	0.692998153
B_Bmem	B cells	IGHA1	0.969434783	D_N_M	Myeloid 1	OLR1	0.641709136	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	MERTK	0.571043006
B_Bmem	B cells	CD79A	0.988008884	D_N_M	Myeloid 1	CD86	0.942643847	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	LIMA1	0.709811988
B_Bmem	B cells	IGLC2	0.987185163	N2_M1_N	Myeloid 4	CSF3R	0.715215998	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	SATB1	0.573754304
B_Bmem	B cells	IGKC	0.994055721	N2_M1_N	Myeloid 4	CXCL2	0.595410915	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	MITF	0.682990431
B_Bmem	B cells	MZB1	0.990953944	N2_M1_N	Myeloid 4	SLC11A1	0.689708163	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	IDS	0.770547371
B_Bmem	B cells	PNOC	0.911511441	N2_M1_N	Myeloid 4	MCEMP1	0.768803468	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	RALGPS2	0.790550186
B_Bmem	B cells	CD27	0.915284037	N2_M1_N	Myeloid 4	TREM1	0.824650671	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	BMPR2	0.81152926
B_Bmem	B cells	FCRL2	0.848730854	N2_M1_N	Myeloid 4	AQP9	0.811375587	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	ACSS2	0.660689281
B_Bmem	B cells	IGHM	0.940097522	N2_M1_N	Myeloid 4	FPR1	0.719975361	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	HNMT	0.588426363
B_Bmem	B cells	JCHAIN	0.952169016	N2_M1_N	Myeloid 4	FPR2	0.737412524	Mast_D_Baso_Bn_MK_T_Th_Bmem	Myeloid 2	HFE	0.379911361
B_Bmem	B cells	TNFRSF13C	0.820399226	N2_M1_N	Myeloid 4	C15orf48	0.570093343	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	CD5L	0.666840631
B_Bmem	B cells	VPREB3	0.870654492	N2_M1_N	Myeloid 4	IL1A	0.820259972	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	NDST2	0.616705557

B_Bmem	B cells	CR2	0.836133953	N2_M_M1_N	Myeloid 4	IL1B	0.695235604	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	PRTN3	0.613580976
B_Bmem	B cells	LY9	0.86687041	N2_M_M1_N	Myeloid 4	CXCL1	0.689400321	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	TLR9	0.614786125
B_Bmem	B cells	CD22	0.943096213	N2_M_M1_N	Myeloid 4	CXCL8	0.75884384	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	IL5	0.718193951
Tgd_T_Tm	non-B Lymphoid 3	IL2RG	0.849230312	N2_M_M1_N	Myeloid 4	S100A8	0.826027987	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	NMBR	0.75771414
Tgd_T_Tm	non-B Lymphoid 3	CD3G	0.881440415	N2_M_M1_N	Myeloid 4	S100A9	0.866857554	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	IZUMO1R	0.665286008
Tgd_T_Tm	non-B Lymphoid 3	CXCR3	0.874962552	N2_M_M1_N	Myeloid 4	IL1RN	0.735164439	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	IL2	0.557187991
Tgd_T_Tm	non-B Lymphoid 3	SH2D1A	0.894351476	N2_M_M1_N	Myeloid 4	LY6D	0.826119538	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	CCL1	0.704954012
Tgd_T_Tm	non-B Lymphoid 3	CD2	0.975933021	N2_M_M1_N	Myeloid 4	CCL7	0.821428177	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	IL21	0.69890301
Tgd_T_Tm	non-B Lymphoid 3	CD3E	0.984355314	N2_M_M1_N	Myeloid 4	OSM	0.782890491	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	TRGV9	0.63922918
Tgd_T_Tm	non-B Lymphoid 3	CD3D	0.895022156	N2_M_M1_N	Myeloid 4	TNF	0.420337801	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	SPIC	0.691740143
Tgd_T_Tm	non-B Lymphoid 3	TRBC2	0.969101205	N2_M_M1_N	Myeloid 4	CSF2	0.593191201	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	TRDV3	0.949214669
Tgd_T_Tm	non-B Lymphoid 3	ITK	0.884268188	Mo_Baso_M_M2_Mast_MK	Myeloid 3	GIMAP4	0.83438145	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	IL26	0.741259723
Tgd_T_Tm	non-B Lymphoid 3	SEPTIN1	0.705468055	Mo_Baso_M_M2_Mast_MK	Myeloid 3	GIMAP5	0.829366114	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	CLEC4C	0.43513567
Tgd_T_Tm	non-B Lymphoid 3	TBC1D10C	0.773429372	Mo_Baso_M_M2_Mast_MK	Myeloid 3	GIMAP1	0.782323816	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	ARG1	0.537690306

Tgd_T_Tm	non-B Lymphoid 3	LCK	0.918259358	Mo_Baso_M_M2_Mast_MK	Myeloid 3	PLAU	0.572969998	Tgd_M2_N2_Th17_Bmem	non-B Lymphoid 2	ADGRG1	0.412855498
Tgd_T_Tm	non-B Lymphoid 3	PDCD1	0.757961539	Mo_Baso_M_M2_Mast_MK	Myeloid 3	HGF	0.595192943				

[0388] *Derivation of TIME genes for clustering*

[0389] To build a gene set for examination of the TIME via clustering that encompasses the diverse genes that might play a role in the TIME in multiple tumor types, TCGA data for eighteen tumor types (lung squamous cell, lung adenocarcinoma, breast, ovarian, kidney clear cell, head and neck, prostate, melanoma, colon, bladder, pancreas, kidney papillary, sarcoma, rectal, B cell lymphoma, kidney chromophobe, esophageal and stomach cancers) were compared to the immune-modulatory, mesenchymal stem like, and mesenchymal TIME subtypes as defined by a 101 gene centroid previously described (Ring, Hout et al. 2016). In an examination of all possible sets of three distinct tumor types among the eighteen tumors, the union of the top 1,000 genes most highly correlated with each subtype were retained for each set of three tumors. These union gene data sets were sorted by the Euclidean distance of the IM, MSL and M clusters, and the top ranked gene sets that included all the eighteen tissues were retained. Gene sets that resulted in skewed cluster sizes which could generate high distances were identified as the standard deviation of the number of genes or tumors divided by the mean of the number of genes or tumors, and gene sets with a value less than 0.7 were not included, resulting in fifteen gene sets. In addition, a list of 27 genes previously described for the identification of the immuno-modulatory tumor environment (Nielsen, Ring et al. 2021) were added, resulting in a final unique gene list with N=2,967.

[0390] *Validation of ImmGen-derived models*

[0391] The ImmGen derived models were validated using defined human immune cell populations GSE22886 (Abbas, Baldwin et al. 2005) and GSE74246 (Corces, Buenrostro et al. 2016). A Student T test was used to determine if the average score for a signature was greater than expected in either the signature's specific cell type (when data was available), or for the lineage of the signature (lymphoid or myeloid). All signatures not further refined by k-means subclasses or tissue of origin were significant when grouped by lineage (lymphoid or myeloid origins) in at least one data set. Those that were significant on both data sets were most of the non-refined signature sets: alpha-beta T cells, mature B cells, all B cells, dendritic cells, granulocytes, and macrophage cells. The CD8+ T cell and gamma-delta T cell models were not significant in both data sets.

[0392] *Description of network models of co-expressed immune markers in relation to other immune signatures*

[0393] In addition to the ImmGen-derived signatures, signatures were also created to identify potential populations of immune cells that may co-infiltrate tumors. These signatures used genes previously declared to be markers for diverse immune cell types and were validated on mouse and human RNASeq data sets of defined cell populations Sets of co-expressed genes across fifteen different tumor types were identified, resulting in eight signatures (Figure 21). These signatures all contained mixtures of immune markers, except for one which was comprised almost entirely of B cell markers (Table 43). However, the genes largely grouped into sets of genes attributed primarily to myeloid, non-B lymphoid, or B cell lineage. These lineage attributions were used to name the signatures, though it should be recognized that these signatures are associated with multiple immune cell types.

[0394] Table 43: Number of unique annotations for different immune cell signatures in each lineage.

Signature	B cell lineage	non-B cell lymphoid lineage	Myeloid lineage
B cells	21	1	0
non-B Lymphoid 1	6	12	6
non-B Lymphoid 2	2	8	8
non-B Lymphoid 3	1	20	1
Myeloid 1	1	1	20
Myeloid 2	3	3	16
Myeloid 3	1	8	13
Myeloid 4	1	1	19

[0395] To further describe the network signatures, they were compared to the signatures derived from the ImmGen data sets across 7,162 samples comprised of 20 tumor types from The Cancer Genome Atlas (Figure 22). Each network signature was compared to all the ImmGen-derived signatures and the correlation of each was contrasted with the correlation of each ImmGen signature to the 27 gene DTIO score previously described for the identification of the immuno-modulatory tumor environment (Nielsen, Ring et al. 2021). In a similar manner, the network signatures were compared to the xCell signatures (Figure 23).

[0396] These comparisons demonstrate and validate that the novel network signatures described herein accurately identify and classify immune infiltrates. As seen in Figure 23, the B cell signature is highly correlated with three xCell B cell signatures, which also are highly correlated with the DTIO score. Diversity between the signatures is shown in these comparisons. The myeloid signature 1 is correlated with three xCell macrophage signatures, as well as a dendritic and monocyte signature, while myeloid signature 4 is associated with two of those xCell macrophage signatures, as well as a granulocyte, monocyte and CD4+ T cell signature. Some of these associated signatures have low correlation with DTIO, suggesting that these network signatures are potentially identifying aspect of the infiltrate population not captured by DTIO. Similarly, the non-B lymphoid network signatures are correlated most strongly with xCell lymphoid signatures, though significant correlations with myeloid signatures are found in all these models. For example, the model non-B lymphoid 2 correlated with a CD8+ and CD4+ T cell signatures, but also with two granulocyte signatures, both of which have a low correlation with DTIO.

[0397] *Distribution of network signatures between tumor tissue and TIME subsets*

[0398] To examine the variation in the prevalence of the tumor samples with high network signature score between tissues and TIME subtypes, the relative proportion of tumor samples have a network signature score higher than the 70th percentile were determined. The samples for a tumor set from The Cancer Genome Atlas (TCGA) were defined as IM, MSL or M subtypes using the 101 gene centroid, as previously described(Ring, Hout et al. 2016). The tumor data was further refined as belonging to the 733 breast samples used for model derivation (training set) or the 359 breast samples reserved as a test set (Figure 24A), the 350 lung adenocarcinoma samples used for model derivation (training set) or the 165 lung adenocarcinoma tumors reserved as a test set (Figure 24B), the 352 lung squamous cell carcinoma samples used for model derivation (training set) or the 149 lung squamous cell carcinomas reserved as a test set (Figure 24C), the 299 colon carcinoma samples used for model derivation (training set) or the 157 colon carcinoma samples reserved as a test set (Figure 24D), and the 270 bladder carcinoma samples used for model derivation (training set) or the 138 bladder carcinoma samples reserved as a test set (Figure 24E).

[0399] Similar proportions of positive samples were seen in both training and test sets in the IM, MSL and M subsets, indicating that the models give consistent results. In adenocarcinoma of the lung, the non-B lymphoid signature 1 had proportions of 0.446 and 0.406 in the IM train and test sets, and 0.271 and 0.255 in the MSL train and test sets (and 0 in both the M subsets). Similarly, the B lymphoid signature had proportions of 0.489 and 0.473 in the IM train and test sets, and 0.257 and 0.194 in the MSL train and test sets (and <0.01 in both the M subsets). In breast carcinoma, the non-B lymphoid signature 1 had proportions of 0.117 and 0.111 in the IM train and test sets, 0.138 and 0.167 in the MSL train and test sets, and 0.027 and 0.028 the M subsets. Similarly, the B lymphoid signature in breast had proportions of 0.109 and 0.106 in the IM train and test sets, 0.147 and 0.175 in the MSL train and test sets, and 0.046 and 0.047 the M subsets.

[0400] However, different proportions were observed between TME subtypes, and between tissues, suggesting that different tumors have different populations of infiltrating immune cells. As expected, IM subtype samples had the greatest prevalence of immune signatures, and M the least. The myeloid signatures frequently had a strong presence in MSL subtype samples, and this relatively increased prevalence also showed variation between tissues. In adenocarcinoma of the lung (Figure 24B), the myeloid 1 signature had a prevalence of 0.251 and 0.218 (train and test) in the MSL subtype, while in lung squamous cell carcinoma the proportions were much lower, at 0.085 and 0.087 (train and test) in the MSL subtype samples. Among other things, this example demonstrates that the TME has a strong role in determining tumor immune infiltrate composition.

[0401] *Distribution of the network signatures in relation to the tumor immune microenvironment*

[0402] To describe the variation in gene expression and distribution of tumor types in relation to the tumor immune microenvironment, we clustered tumor samples comprising 20 tumor types from The Cancer Genome Atlas (TCGA; https://portal.gdc.cancer.gov/) using the training set of cases. A list of 2,967 genes derived (as described herein) to highlight distinct molecular physiologies across the TIME expression landscape were used for clustering. Genes and tumor samples were initially grouped by their correlation to the IM, MSL and M tumor subtypes, and then hierarchically clustered. Annotation of genes by protein families is shown, and each tumor sample is annotated with the correlation to the IM,

MSL and M subtypes using the 101 gene centroid models, as well as the 27 gene DTIO score and call. Clusters using the 4,883 training samples (Figure 25A), the 2,279 test samples (Figure 25B), and the complete set of 7,162 samples (Figure 25C) are shown.

[0403] The distribution of the lymphoid and myeloid network signatures in relation to these clusters is shown for the training samples (Figure 26A and Figure 26B), the test samples (Figure 26C and Figure 26D), and all samples (Figure 26E and Figure 26F). The score of the network signatures is shown, and large peaks above their mean value are highlighted. To identify groups of tumors in which DTIO may not be capturing information about immune cell infiltrate presences, the degree of agreement for the signature and DTIO, defined as the min-max normalization of the network score subtracted from the min-max normalization of the DTIO score, was also shown.

[0404] There is considerable variation between the network signatures across the TIME. The B cell, and non-B lymphoid signatures 1 and 3 show an overall similarity, but non-B lymphoid signature is relatively distinct, especially in the MSL subset. The Pearson correlation of the B lymphoid signature with DTIO across the training and set samples was 0.46 and 0.45, in non-B lymphoid 1 it was 0.51 and 0.50, and in non-B lymphoid 3 it was 0.64 and 0.63, while in non-B lymphoid 2 it was 0.38 and 0.37 (train and test sets). They myeloid signature showed even greater differences with DTIO, with myeloid 2 and 3 have correlations with DTIO of -0.06 and -0.01 (train and test) and 0.099 and 0.12 (train and test), respectively.

[0405] *Association of network signatures with outcome in ICI treated patients*

[0406] To compare the association of outcome of several immune signatures, all derived ImmGen and network signatures, as well as the immune signatures from the xCell study, were applied to cohort 2 (platinum treated) of the Imvigor 210 trial (Suzman, Agrawal et al. 2019). Significant signatures are shown in Table 44, and were assessed on a bladder cohort (GSE176307)(Rose, Weir et al. 2021), and a melanoma cohort (GSE91061)(Riaz, Havel et al. 2017). The melanoma cohort was analyzed both before treatment with Nivolumab and after four weeks of treatment. Of the immune signatures that were significant on the Imvigor 210 cohort, only DTIO and the two network signatures (B cell signature and non-B lymphoid signature 3) were significant on the bladder and

melanoma cohorts. It is interesting that the only xCell signatures to be significant in the Imvigor cohort, and are also significant in the melanoma cohort, are T cell signatures, which might have a relationship with the network model non-B Lymphoid 3, and plasma cells, and may reflect the significance of the network B cell signature.

[0407] Table 44: Significant immune infiltrate signatures from Imvigor 210 trial data.

	Imvigor 210 cohort 2 (bladder, 2 year OS)			GSE176307 (bladder, 1 year OS)			GSE91061 Pre-treatment (melanoma, response)			GSE91061 On treatment (melanoma, response)		
Signature	**N**	**OR (95% CI)**	**P value**	**N**	**beta (95% CI)**	**P value**	**N**	**beta (95% CI)**	**P value**	**N**	**beta (95% CI)**	**P value**
DTIO	272	**0.28 (0.15-0.5)**	**< 0.0001**	89	**0.02 (0-0.39)**	**0.0115**	49	1.89 (-1.82-5.6)	0.0952	56	**2.72 (-2.61-8.06)**	**0.0215**
Network: B cells	272	**0.91 (0.83-1)**	**0.05**	89	**0.8 (0.67-0.97)**	**0.0218**	49	0.22 (-0.21-0.64)	0.1051	56	**0.5 (-0.48-1.48)**	**0.0005**
Network: non-B Lymphoid 3	272	**0.87 (0.78-0.97)**	**0.01**	89	**0.72 (0.57-0.9)**	**0.0051**	49	0.29 (-0.28-0.85)	0.0804	56	**0.53 (-0.51-1.57)**	**0.0029**
ImmGen: CD8+ activated T cells	272	**1.34 (1.06-1.68)**	**0.01**	89	1.15 (0.86-1.55)	0.351	49	0.1 (-0.09-0.29)	0.8155	56	0.28 (-0.27-0.84)	0.3943
ImmGen: Macrophage	272	**1.5 (1.2-1.88)**	**0**	89	0.78 (0.5-1.22)	0.2788	49	-0.22 (0.22--0.66)	0.3759	56	-0.01 (0.01--0.04)	0.9606
xCell: CD8+ central memory T cell	272	**< 0.001 (< 0.001-0.88)**	**0.05**	89	< 0.001 (< 0.001 - >100)	0.203	49	**7.49 (-7.19-22.16)**	**0.0482**	56	**6.49 (-6.23-19.21)**	**0.0029**
xCell: CD8+ effector memory T cell	272	**< 0.001 (< 0.001-0.4)**	**0.04**	89	< 0.001 (< 0.001->100)	0.4258	49	31.52 (-30.26-93.3)	0.1167	56	**17.84 (-17.13-52.82)**	**0.0019**
xCell: Plasma cells	272	**< 0.001 (< 0.001-0.54)**	**0.04**	89	< 0.001 (< 0.001->100)	0.1822	49	18.93 (-18.17-56.04)	0.4096	56	**47.42 (-45.53->100)**	**0.0232**
xCell: T gamma-delta cells	272	**< 0.001 (< 0.001-0)**	**0**	89	< 0.001 (< 0.001->100)	0.1026	49	29.37 (-28.19-86.93)	0.1259	56	**32.25 (-30.96-95.47)**	**0.0214**

[0408] The similar prognostic capabilities of DTIO and these two network signatures can be observed in Kaplan-Meier plots of the overall survival of patients with high network B cell signature and non-B lymphoid 3 scores (defined as above or below the mean of the study population) was observed for two year overall survival in Imvigor (N=272) (Figure 27A and Figure 27B) and the other bladder cohort (GSE176307, N=89) (Figure 27C and Figure 27D. As expected from the similarity in distributions of scores of these signatures with DTIO, each captures much of the prognostic ability of DTIO.

[0409] Among other things, the present example demonstrates methods for identification of novel immune infiltrate populations within tumor samples (*e.g.*, within tumor immune microenvironment (TIME)). In some embodiments, methods provided herein may be used to determine immune infiltrate levels for a particular tumor type without the need for a solid tumor biopsy. In some embodiments, immune infiltrate information provided herein may be used to inform or select one or more therapies for a tumor. In some embodiments, immune infiltrate information provided herein may be used in combination with tumor gene expression subtype data and/or DetermaIO scoring to inform or select one or more therapies for a tumor. In some embodiments, immune infiltrate information provided herein may be used in combination with tumor gene expression subtype data and/or DetermaIO scoring to identify patients whose cancer may not be adequately met by existing therapeutic regimens, or otherwise are strong candidates for novel drug discovery and development programs.

Equivalents

[0410] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the following claims:

Claims

We claim:

1. A method of treating cancer, the method comprising a step of:

administering immunomodulation therapy to subjects whose tumors have been determined to be responsive to the immunomodulation therapy by assessment of both:

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status;

wherein the subtype markers are considered to indicate likely non-responsiveness to immunomodulation therapy and the status markers are considered to indicate likely responsiveness to immunomodulation therapy.

2. A method of assessing a tumor's likely responsiveness to immunomodulation therapy, which method comprises

(a) assessing both:

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status; and

(b) calculating, by means of a computer, an IO score by weighting the subtype markers as likely to indicate non-responsiveness to immunomodulation therapy and the status markers as likely to indicate responsiveness to immunomodulation therapy.

3. The method of claim 2, further comprising a step of administering the immunomodulation therapy to a subject whose tumor has been determined to have an IO score above a threshold established to correlate with responsiveness to the immunomodulation therapy.

4. The method of claim 2, further comprising a step of administering an alternative therapy to a subject whose tumor has been determined to have an IO score below a certain threshold.

5. The method of claim 3, wherein the immunomodulation therapy is selectively administered to subjects whose tumors have been determined to have IO scores above a certain threshold.

6. The method of claim 3, wherein the immunomodulation therapy is selected from the ICI therapy, CAR-T cell therapy, neoantigen vaccine therapy, or combinations thereof.

7. The method of claim 4, wherein the alternative therapy is kinase inhibitor or other tumor microenvironment modulating therapy.

8. A method of monitoring therapy administered to a cancer patient, the method comprising steps of:

(a) at each of a plurality of time points, determining both

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status;

wherein the subtype markers are considered to indicate likely non-responsiveness to immunomodulation therapy and the status markers are considered to indicate likely responsiveness to immunomodulation therapy, so that an IO score representing the patient's likelihood of responding to the immunomodulation therapy is determined; and

(b) adjusting therapy in light of a change in the IO score.

9. A method of treating a tumor, which method comprises steps of:

(a) at a first time point, assessing the tumor by determining both

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status;

wherein the subtype markers are considered to indicate likely non-responsiveness to immunomodulation therapy and the status markers are considered to indicate likely responsiveness to immunomodulation therapy, so that an IO score representing the tumor's likelihood of responding to the immunomodulation therapy is determined;

(b) selecting therapy according to the IO score, wherein the selecting comprises:

(i) initiating or continuing immunomodulation therapy when the IO score meets a threshold determined to correlate with responsiveness to the immunomodulation therapy; and/or

(ii) reducing or withdrawing the immunomodulation therapy and/or initiating or continuing alternative therapy when the IO score meets a threshold determined to correlate with non-responsiveness to the immunomodulation therapy.

10. The method of claim 8, wherein an increase in IO score, or an IO score greater than a predefined threshold, indicates an increased likelihood of responding to the immunomodulation therapy.

11. The method of claim 8, wherein a decrease in IO score, or an IO score less than a predefined threshold, indicates a reduced likelihood of responding to the immunomodulation therapy.

12. The method of claim 8, wherein the immunomodulation therapy is selected from the ICI therapy, CAR-T cell therapy, neoantigen vaccine therapy, or combinations thereof.

13. The method of claim 8, wherein the alternative therapy is kinase inhibitor therapy.

14. A method comprising steps of:

a. receiving, by a processor of a computing device, data corresponding to levels of a plurality of markers for each of:
    i. a subtype selected from M, MSL, and combinations thereof; and
    ii. an IM status;
b. automatically determining, by the processor, a classification of the subject as non-responsive to a first therapy (e.g. immunomodulation therapy) using the data received in step (a) to produce a numerical score; and, optionally,
c. prescribing and/or administering a second therapy (e.g. an alternative to the first therapy, e.g., an alternative to immunomodulation therapy) to the subject

for treatment of the disease, thereby avoiding prescription and/or administration of the first therapy to the subject.

15. A method comprising the steps of:

a. receiving, by a processor of a computing device, data corresponding to levels of a plurality of markers for each of:
    i. a subtype selected from M, MSL, and combinations thereof; and
    ii. an IM status;
b. automatically determining, by the processor, a classification of the subject as responsive to a first therapy (e.g. immunomodulation therapy) using the data received in step (a) to produce a numerical score; and, optionally,
c. prescribing and/or administering the first therapy to the subject for treatment of the disease.

16. In a method of administering an immunomodulation therapy, the improvement that comprises administering the therapy selectively to subjects who have been assigned a numerical IO score calculated through assessment of each of:

a. Mesenchymal (M) subtype and/or mesenchymal stem-like (MSL) subtype as a negative predictor of responsiveness; and
b. IM status as a positive predictor of responsiveness.

17. The method of claim 16, wherein the assigned IO score is above a threshold established to distinguish between responsive and non-responsive historical subjects who have received the immunomodulation therapy.

18. A method of determining a tumor classifier effective to distinguish between responsiveness and non-responsiveness to immunomodulation therapy, the method comprising steps of:

a. Employing elastic net regularized linear models to create individual subclassifying models for a set of subtypes;

b. Training the classifier on a gene expression dataset from a sample of interest; and

c. Assessing the correlation between the classifier and responsiveness to immunomodulation therapy.

19. The method of claim 18, wherein the classifier comprises a set of between 75 and 100 genes.

20. The method of claim 18, wherein the classifier comprises a set of between 50 and 75 genes.

21. The method of claim 18, wherein the classifier comprises a set of between 25 and 50 genes.

22. The method of claim 18, wherein the classifier comprises a set of less than 25 genes.

23. The method of claim 18, wherein the subtypes are defined based upon previously established models.

24. The method of claim 23, wherein the classifier comprises a reduced gene set compared to previously established models.

25. A method of treating cancer, the method comprising steps of:

(i) assessing expression levels for one or more genes selected from the group consisting of :

CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1., CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS,

RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1, SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5, TNFAIP8, TNFSF10, RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG, CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273, CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6, KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2, APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1, ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16, GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3, HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R, BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1, C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3, FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1, ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12, MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2, ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1, TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1, ITGBL1, ASPN, PDGFRB, HTRA1, HEG1, ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1, TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19, ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1,

TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, and ZCCHC24;

(ii) comparing the assessed expression with a set of reference thresholds for the one or more genes; and

(iii) administering ICI therapy to the subject if the comparing determines that the assessed expression levels have a significant pattern relative to their reference thresholds.

26. A method of assessing a tumor's likely responsiveness to immunomodulation therapy, which method comprises

(a) assessing both:

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status; and

(b) calculating, by means of a computer, an IO score by weighting the subtype markers as likely to indicate non-responsiveness to immunomodulation therapy and the status markers as likely to indicate responsiveness to immunomodulation therapy;

wherein the subtype markers and status markers are expression levels for a set of genes selected from the group consisting of:

CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1., CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1, SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5, TNFAIP8, TNFSF10, RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG, CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273, CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6, KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2, APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1, ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16, GZMB,

GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3, HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R, BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1, C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3, FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1, ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12, MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2, ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1, TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1, ITGBL1, ASPN, PDGFRB, HTRA1, HEG1, ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1, TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19, ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24, and combinations thereof.

27. The method of claim 26, wherein the subtype markers and status markers comprise at least one gene from one or more gene groups below:

Group A: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1;

Group B1: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10;

Group B2: COL2A1, FOXC1, KRT16, MIA, SFRP1;

Group B3: APOD, ASPN, HTRA1;

Group C1: SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5;

Group C2: TNFAIP8, TNFSF10;

Group C3: RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG;

Group C4: CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273;

Group C5: CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6;

Group C6: KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2;

Group C7: APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1;

Group C8: ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16;

Group C9: GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3;

Group C10: HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R;

Group C11: BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1;

Group C12: C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3;

Group C13: FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1;

Group C14: ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12;

Group C15: MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2;

Group C16: ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1;

Group C17: TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1;

Group C18: ITGBL1, ASPN, PDGFRB, HTRA1, HEG1;

Group C19: ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1;

Group C20: TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19; and

Group D1: ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24.

28. The method of claim 27, wherein the subtype markers and status markers comprise at least one gene from five or more of the gene groups.

29. The method of claim 28, wherein the subtype markers and status markers comprise at least one gene from ten or more of the gene groups.

30. The method of claim 29, wherein the subtype markers and status markers comprise at least one gene each of the gene groups

31. The method of claim 27, wherein the subtype markers and status markers comprise:
(i) at least one gene selected from Group A;
(ii) at least one gene selected from any one of Group B1, Group B2, or Group B3;
(iii) at least one gene selected from any one of Group C1, Group C2, Group C3, Group C4, Group C5, Group C6, Group C7, Group C8, Group C9, Group C10, Group C11, Group C12, Group C13, Group C14, Group C15, Group C16, Group C17, Group C18, Group C19, Group C20; and
(iv) at least one gene selected from Group D1.

32. The method of claim 2, further comprising a step of administering an additional therapy to a subject whose tumor has been determined to have an IO score below a certain threshold.

33. The method of claim 32, wherein the additional therapy is selected to target gene pathways associated with negative IO scores.

34. The method of claim 33, wherein the immunomodulation therapy is ICI therapy and the additional therapy is not ICI therapy.

35. The method of claim 33, wherein the immunomodulation therapy and additional therapy are co-administered.

36. The method of claim 33, wherein the immunomodulation therapy and additional therapy are administered sequentially.

37. The method of claim 4, wherein the alternative therapy is selected to target gene pathways associated with negative IO scores.

38. The method of claim 37, wherein the immunomodulation therapy is ICI therapy and the alternative therapy is not ICI therapy.

39. The method of claim 37, wherein:

(i) the alternative therapy is administered; and

(ii) the IO score is determined after alternative therapy administration;

wherein,if the IO score has changed to be above a certain threshold, the alternative therapy is either:

discontinued in favor of immunomodulation therapy; or

continued along with co-administration of immunomodulation therapy.

40. A method of establishing a biomarker indicative of immune microenvironment status, the method comprising steps of:

determining a correlation between a candidate biomarker and one or more of IM status markers and M and MSL subtype markers;

incorporating the candidate biomarker into a complete biomarker that includes both indicators of likely responsiveness and indicators of likely non-responsiveness to immunomodulation therapy.

41. The method of claim 40, wherein the IM status markers and the M and MSL subtype markers comprise at least one gene from one or more gene groups below:

Group A: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1;

Group B1: CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10;

Group B2: COL2A1, FOXC1, KRT16, MIA, SFRP1;

Group B3: APOD, ASPN, HTRA1;

Group C1: SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5;

Group C2: TNFAIP8, TNFSF10;

Group C3: RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG;

Group C4: CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273;

Group C5: CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6;

Group C6: KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2;

Group C7: APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1;

Group C8: ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16;

Group C9: GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3;

Group C10: HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R;

Group C11: BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1;

Group C12: C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3;

Group C13: FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1;

Group C14: ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12;

Group C15: MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2;

Group C16: ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1;

Group C17: TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1;

Group C18: ITGBL1, ASPN, PDGFRB, HTRA1, HEG1;

Group C19: ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1;

Group C20: TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19; and

Group D1: ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24.

42. The method of claim 40, wherein the IM status markers and the M and MSL subtype markers are identified by a gene expression algorithm.

43. The method of claim 40, wherein the biomarker comprises one or more gene variants.

44. The method of claim 43, wherein the one or more gene variants may present differences in gene expression.

45. A method of treating cancer, the method comprising steps of:

(i) assessing expression levels in a sample from a subject suffering from the cancer, for a set of genes selected from the group consisting of :

CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1., CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1, SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5, TNFAIP8, TNFSF10, RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG, CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273, CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6, KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2, APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1, ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16, GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3, HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R, BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1, C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3, FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1, ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12, MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2, ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1, TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1, ITGBL1, ASPN, PDGFRB, HTRA1, HEG1, ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1, TCF7L1,

CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19, ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7, FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24, and combinations thereof,

wherein reference levels for the set have been established, when considered together, to characterize M, IM and MSL character; and

(ii) comparing the assessed expression levels with the set of established reference levels; and; and

(iii) administering ICI therapy to the subject if the comparing determines that the assessed expression levels indicate that the M, IM, and MSL character of the subject's cancer indicate that it is likely to be responsive to the ICI therapy.

46. A method of establishing a biomarker indicative of immune microenvironment status, the method comprising steps of:

providing a classification system that includes both:

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status; and

has been established to predict responsiveness to immunomodulation therapy by considering both markers that indicate likely non-responsiveness and markers that indicate likely responsiveness to the immunomodulation therapy.

47. The method of claim 46, wherein the markers are or comprise expression levels for a set of genes selected from the group consisting of;
CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1., CCL5, CD52, CXCL11, CXCL13, DUSP5, GZMB, IDO1, IL23A, ITM2A, KMO, KYNU, PSMB9, PTGDS, RARRES3, RTP4, S100A8, SPTLC2, TNFAIP8, TNFSF10, COL2A1, FOXC1, KRT16, MIA, SFRP1, APOD, ASPN, HTRA1, SAMSN1, CD80, CLEC7A, PDCD1LG2, CD274, S100A8, KYNU, LINC02195, IL9R, DUSP5, TNFAIP8, TNFSF10, RARRES3, APOL3, LINC02446, ZNF683, IFNG, FASLG, CD48, CD52, C16orf54, TESPA1, JAML, GMFG, ARHGAP15, TMEM273, CD3G, TIGIT, SIRPG, TRAC, CD3E, CD2, TRBV28, CD3D, TRBC2, CCR5, CD8A, CCL5, IL2RB, CXCR6, KMO, SNX10, PIK3AP1, SLC7A7, VCAM1, RASSF4, TFEC, HAVCR2, APOL6, IDO1, CXCL9, GBP5, GBP1, GBP4, CXCL11, CXCL10, LAP3, STAT1, WARS1, SAMHD1, ZBP1, OASL, EPSTI1, IL15RA, USP30-AS1, BATF2, ETV7, PSMB10, RTP4, CARD16, GZMB, GZMH, GNLY, CD8B, CTSW, CST7, NKG7, GZMA, PRF1, CD247, SLA2, PDCD1, CD7, LAG3, HNRNPA1P21, FOXP3, CCR8, CXCL13, AIM2, IL2RA, ICOS, CTLA4, TNFRSF9, IL21R, BTN3A3, BTN3A1, TAP2, NLRC5, HLA-F, PSMB8, PSMB9, TAP1, HCP5, UBE2L6, PSME2, IRF1, C19orf38, IGFLR1, LINC01943, RAB33A, SLC2A6, IFI30, LILRB3, IL23A, PSME2P2, ITGAE, STAC3, FOXC1, ADAMTS9-AS2, RGN, KL, ADAMTS9-AS1, WDFY3-AS2, PTH1R, PLEKHH2, WSCD1, CABP1, CEP112, TMEM47, RCAN2, LIN7A, LEPR, PDGFA, SERTAD4-AS1, ADH1B, C7, CCL14, SELP, ACKR1, MMRN1, ITM2A, AQP1, ABI3BP, P2RY12, MPRIP, KIF13B, FYCO1, SPTLC2, ADGRA3, RBFOX2, ITGB4, KRT17, KRT16, KRT14, KRT5, DSG3, COL17A1, TMEM119, PODN, SVEP1, LAMA2, COL14A1, FGF7, OGN, PRELP, ELN, MFAP4, SSC5D, PTGDS, CHRDL1, ITGBL1, ASPN, PDGFRB, HTRA1, HEG1, ZCCHC24, SGCD, SRPX, APOD, SHC4, MIA, IL17D, LRRN4CL, BOC, PDZRN3, SFRP1, TCF7L1, CACNA1G, SPEG, COL2A1, CRISPLD1, PIANP, NACAD, EFNB3, PCYT1B, RGMA, GLI2, PCDH19, ABCA8, ADRA2A, AKAP12, ALDH3B2, APOD, ART3, ASPN, AZGP1, BLVRB, C7, CCL5, CD36, CD52, CDC20, CHI3L1, COL2A1, COL5A1, COL5A2, CRAT, CROT, CXCL10, CXCL11, CXCL13, CYP4F8, DBI, DEFB1, DHCR24, DUSP5, FABP7,

FASN, FGFR4, FGL2, FOXA1, FOXC1, GABRP, GALNT7, GBP1, GCHFR, GPR87, GZMB, HGD, HTRA1, IDO1, IGFBP4, IGHM, IGJ, IL23A, IL33, INPP4B, ITM2A, JAM2, KCNK5, KIAA1324, KMO, KRT14, KRT16, KRT17, KRT6A, KRT6B, KYNU, LBP, LHFP, IGKC, MFAP4, MIA, MID1, MYBL1, NEK2, NTN3, OGN, PI3, PLEKHB1, PMAIP1, PSMB9, PTGDS, RARRES3, RTP4, S100A1, S100A7, S100A8, SCRG1, SEMA3C, SERHL2, SFRP1, SIDT1, SOX10, SPDEF, SPRR1B, SPTLC2, SRPX, TCF7L1, TFAP2B, THBS4, TNFAIP8, TNFSF10, TRIM68, TSC22D3, UBD, UGT2B28, XBP1, ZCCHC24, and combinations thereof.

48. The method of claim 46, wherein the markers are or indicate, presence or level of a particular form of one or more genes or gene products.

49. The method of claim 47 or claim 48, wherein the candidate biomarker is selected from the group consisting of presence and level of a particular form of a gene or gene product.

50. The method of claim 49 wherein the candidate biomarker is or comprises presence or level of one or more miRNA species.

51. The method of claim 49, wherein the candidate biomarker is or comprises presence or level of one or more epigenetic modifications.

52. The method of claim 49, wherein the candidate biomarker is or comprises presence or level of one or more gene mutations.

53. The method of claim 49, wherein the candidate biomarker is or comprises presence or level of one or more gene transcript forms.

54. The method of claim 49, wherein the candidate biomarker is or comprises presence or level of one or more proteins or forms thereof.

55. A method of characterizing a potential cancer therapy by determining that it directly or indirectly correlates with an immunomodulatory (IM) status or with a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL).

56. A method comprising a step of:
detecting in a subject who is a candidate for receiving a particular therapy a biomarker established to correlate with responsiveness or non-responsiveness to the therapy.

57. A method of treating a subject in whom a biomarker has been detected, the method comprising steps of:
administering immunomodulation therapy or therapy that sensitizes to immunomodulation therapy if the therapy has been correlated with IM status; and
administering alternative therapy if the biomarker has been correlated with M or MSL subtype.

58. A method of treating a subject in whom a biomarker has been detected, the method comprising steps of:
administering therapy that has been correlated with IM status if the biomarker has also been so correlated; and
administering therapy that has been correlated with M or MSL subtype if the therapy has also been so correlated.

59. The method of claim 46, wherein the candidate biomarker is or comprises a gene comprising one or more mutations.

60. A method of treating a subject, comprising steps of:
(a) assessing a biomarker indicative of immune microenvironment status; and
(b) selecting a treatment option based upon biomarker level.

61. A method of claim 60, wherein the assessment of a biomarker includes:
(a) assessing both:

(i) subtype markers of a subtype selected from mesenchymal (M), mesenchymal stem-like (MSL), and combinations thereof; and

(ii) status markers of immunomodulatory (IM) status; and

(b) calculating, by means of a computer, an IO score by weighting the subtype markers as likely to indicate non-responsiveness to immunomodulation therapy and the status markers as likely to indicate responsiveness to immunomodulation therapy.

62. The method of claim 60 or 61, wherein the biomarker is or comprises presence or level of a particular form of one or more genes or gene products

63. The method of claim 62, wherein the one or more genes or gene products comprise one or more mutations.

64. The method of claim 62, wherein the one or more genes or gene products comprise one or more methylated genes.

65. The method of claim 64, wherein the assessing comprises assessment of methylation status and/or level.

66. The method of claim 60 or 61, wherein the biomarker is or comprises presence or level of one or more miRNA species.

67. The method of claim 66, wherein the biomarker is a miRNA present in blood.

68. The method of claim 66, wherein the biomarker is a miRNA present in a solid tumor.

69. The method of claim 60 or 61, wherein the biomarker is or comprises one or more immune cell types.

70. The method of claim 60 or 61, wherein the biomarker is or comprises one or more immune cell types.

71. The method of claim 62, wherein the gene or gene products are correlated with one or more immune cell types.

72. The method of any one of claims 60-71, wherein the treatment option comprises administration of one or more compounds.

73. The method of claim 72, wherein the subject is determined to have a tumor type sensitive to the one or more compounds.

74. The method of claim 72, wherein the subject is determined to have a tumor type with a particular IO score that may change upon administration of the one or more compounds.

75. The method of claim 74, wherein the treatment option further comprises co-administration or sequential administration of an additional or alternative therapy based upon change in IO score.

76. The method of claim 60, wherein:

the biomarker is determined to have a correlation with one or more M or MSL subtype markers; and

the biomarker is determined to have biochemical, physical, or regulatory interactions with one or more additional biomarkers determined to have a correlation with one or more IM status markers.

77. The method of claim 60, wherein:

the biomarker is determined to have a correlation with one or more IM status markers; and

the biomarker is determined to have biochemical, physical, or regulatory interactions with one or more additional biomarkers determined to have a correlation with one or more M or MSL subtype markers.