

method selected from a PCR method, a microarray method, or an immunoassay method. In one embodiment, the microarray method comprises the use of a microarray chip having one or more nucleic acid molecules that can hybridize under stringent conditions to a nucleic acid molecule encoding a gene mentioned above or having one or more polypeptides (such as peptides or antibodies) that can bind to one or more of the proteins encoded by the genes mentioned above. In one embodiment, the PCR method is qPCR. In one embodiment, the PCR method is multiplex-PCR. According to one embodiment, the immunoassay method comprises binding an antibody to protein expressed from a gene mentioned above in a patient sample and determining if the protein level from the patient sample is elevated. In certain embodiments, the immunoassay method is an enzyme-linked immunosorbent assay (ELISA).

[0019a] In one embodiment, there is provided a method of prognosing or of aiding prognosis of IPF in a patient comprising determining a total baseline biomarker score in a biological sample obtained from the patient, wherein the determining of the total baseline biomarker score comprises measuring the protein expression level of COMP and at least one of CXCL13 and OPN, and assigning a score of 0 if the expression level is below the median for CXCL13, OPN, and COMP, respectively, and assigning a score of 1 if the expression level is above the median for CXCL13, OPN, and COMP, respectively, wherein the determining of the total baseline biomarker score further comprises measuring the protein expression level of YKL-40 and assigning a score of 0 if the expression level is below the median for YKL-40 and assigning a score of 1 if the expression level is above the median for YKL-40, and wherein the determining of the total baseline biomarker score further comprises adding each individual score to obtain the total baseline biomarker score, wherein a total baseline biomarker score of two or above is indicative of a prognosis of shortened survival compared to median survival and wherein a total baseline biomarker score of zero or one is indicative of a prognosis of increased survival compared to the median survival.

[0020] In another embodiment, methods of prognosing or of aiding prognosis of IPF in a patient are provided where a biological sample is obtained from the patient and a total baseline biomarker score is determined. In certain embodiments, the determining of the total baseline biomarker score comprises measuring the protein expression level of at least one of CXCL13, OPN, and COMP and assigning a score of 0 if the expression level is below the median for CXCL13, OPN, and COMP, respectively, and assigning a score of 1 if the expression level is above the median for CXCL13, OPN, and COMP, respectively, wherein the determining of the total baseline biomarker score further comprises measuring the protein

(FG-3019), anti-CCL2 antibody (CNTO 888), somatostatin analog (SOM230, octreotide), antiotensin II inhibitor (losartan), carbon monoxide, thalidomide, tetrathiomolybdate, doxycycline, minocycline, and tyrosine kinase inhibitor (BIBF1120). In one embodiment, the anti-IL-13 agent is lebrikizumab. In one embodiment, the anti-IL-13/anti-IL-4 agent is a bispecific antibody. In one embodiment, the anti-IL-13 agent is an anti-IL-13 antibody comprising three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL-13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL-13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14. In certain embodiments, methods of treating an IPF patient are provided where an effective amount of an IPF therapeutic agent as provided above is administered provided that the patient has a baseline score of two or above determined according to the methods described above.

[0021a] In one embodiment, there is provided a method of prognosing or of aiding prognosis of IPF in a patient comprising determining a total baseline biomarker score in a biological sample obtained from the patient, wherein the determining of the total baseline biomarker score comprises measuring the protein expression level of COMP or MMP3 and COMP, and assigning a score of 0 if the expression level is below the median for MMP3 and COMP, respectively, and assigning a score of 1 if the expression level is above the median for MMP3 and COMP, respectively, wherein the determining of the total baseline biomarker score further comprises measuring the protein expression level of YKL-40 and assigning a score of 0 if the expression level is below the median for YKL-40 and assigning a score of 1 if the expression level is above the median for YKL-40, and wherein the determining of the total baseline biomarker score further comprises adding each individual score to obtain the total baseline biomarker score, wherein a total baseline biomarker score of one or above is indicative of a prognosis of shortened survival compared to median survival and wherein a total baseline biomarker score of zero is indicative of a prognosis of increased survival compared to the median survival.

and SAA4, and elevated expression of the one or the combination of genes, or elevated expression of the one or the combination of proteins, is indicative of the IPF molecular subtype. In certain embodiments, the one or the combination of genes is selected from CXCR3, CXCR5, CXCL13, CCR6, CCR7, CD19, MS4A1 (CD20), TNFRSF17 (BCMA), BLK, BLNK, FCRLA, FCRL2, FCRL5, CD79A, CD79B, CD27, CD28, CD1A, CD1B, CD1C, CD1E, IGHV1-69, IGLJ3, IGJ, IGHV3-48, IGLV3-21, IGKV1-5, IGHG1, IGKC, IGLV6-57, IGK@ (immunoglobulin kappa locus), IGHA1, IGKV2-24, IGKV1D-8, IGHM, and elevated expression of the one or the combination of genes, or elevated expression of the one or the combination of proteins, is indicative of the IPF molecular subtype. In certain embodiments, the one or the combination of genes is selected from COL1A1, COL1A2, COL5A2, COL12A1, COL14A1, COL15A1, COL16A1, COL18A1, CTHRC1, HGF, IGFBP7, SCGF (CLEC11A); LOXL1, LOXL2; GLI1, GLI2, SMO; SFRP2, DIO2, CDH11, POSTN, and TGFB3, and elevated expression of the one or the combination of genes, or elevated expression of the one or the combination of proteins, is indicative of the IPF molecular subtype. In certain embodiments, the gene expression level is measured by assaying for mRNA levels. In certain embodiments, the assay comprises a PCR method and/or the use of a microarray chip. In one embodiment, the PCR method is qPCR. In one embodiment, the PCR method is multiplex-PCR. In certain embodiments, kits include at least one enzyme selected from a nuclease, a ligase, and a polymerase. In certain embodiments, the protein expression level is measured by an immunoassay. In certain embodiments, immunoassay kits are provided comprising one or more antibodies that bind to one or more proteins encoded by one of the genes identified above.

[0025] In another embodiment, the biological sample for use according to any of the above methods is lung tissue, whole blood, or serum. In certain embodiments, the biological sample is lung tissue or whole blood and the expression of the one or the combination of genes is measured using a PCR method or a microarray chip. In certain embodiments, the biological sample is serum and the expression of the one or the combination of proteins is measured using an immunoassay.

[0026] In yet still another embodiment, methods of treating IPF in a patient are provided.

[0026a] In certain embodiments, the methods comprise administering an effective amount of an IPF therapeutic agent to the patient to treat the IPF, provided that elevated expression of one or a combination of genes, or expression of one or a combination of proteins encoded by the one or the combination of genes, has been detected in a biological sample obtained from the patient. In one embodiment, the one or the combination of genes is selected from MUCL1,

kinase inhibitor (BIBF1120). In certain embodiments, the IPF therapeutic agent is an anti-IL-13 antibody. In one embodiment, the anti-IL-13 agent is an anti-IL-13 antibody comprising three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL-13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL-13 antibody (lebrikizumab) comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14. In certain embodiments, lebrikizumab is administered subcutaneously once every four weeks at a flat dose selected from 125 mg, 250 mg, and 500 mg. In one embodiment, lebrikizumab is administered subcutaneously once every four weeks at a flat dose of 250 mg.

[0026a] In a second aspect, there is provided the use of an IPF therapeutic agent in the manufacture of a medicament for the treatment of an IPF patient previously determined to have a prognosis of shortened survival according to the methods as defined herein.

[0027] In one embodiment, methods of treating an IPF patient previously determined to have a prognosis of shortened survival according to the methods above are provided. In certain such embodiments, an effective amount of the IPF therapeutic agent is administered. In one embodiment, the IPF therapeutic agent is selected from an anti-IL-13 agent, an anti-IL-4 agent, a combination anti-IL-13/anti-IL-4 agent, pirfenidone, anti-LOXL2 antibody (GS-6624), N-acetylcysteine, anti-TGF- β antibody (GC1008), anti- α v β 6 integrin antibody (STX-100), anti-CTGF antibody (FG-3019), anti-CCL2 antibody (CNTO 888), somatostatin analog (SOM230, octreotide), antiotensin II inhibitor (losartan), carbon monoxide, thalidomide, tetrathiomolybdate, doxycycline, minocycline, and tyrosine kinase inhibitor (BIBF1120). In one embodiment, the anti-IL-13 agent is an anti-IL-13 antibody comprising three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL-13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL-13 antibody (lebrikizumab) comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid

CLAIMS

WHAT IS CLAIMED IS:

1. A method of prognosing or of aiding prognosis of idiopathic pulmonary fibrosis (IPF) in a patient comprising measuring in a biological sample obtained from the patient the expression of a combination of three or more genes, or expression of a combination of three or more proteins encoded by the combination of three or more genes, wherein the three or more genes are selected from COMP, MMP3, YKL-40, CXCL13, SAA4 (constitutive SAA) and SPP1 (OPN), wherein the combination of three or more genes comprises MMP3, wherein an elevated expression level of the combination of three or more genes, or an elevated expression level of the combination of three or more proteins, is indicative of a prognosis for shortened survival compared to median survival and wherein a reduced expression level of the combination of three or more genes, or a reduced expression level of the combination of three or more proteins, is indicative of a prognosis for increased survival compared to median survival.
2. The method of claim 1, wherein the combination of three or more genes comprises YKL-40.
3. The method of claim 1, wherein the combination of three or more genes further comprises MMP7.
4. The method of claim 1, wherein the combination of three or more genes further comprises a gene selected from CCL11, CCL13, CCL17, and CCL18.
5. The method of claim 1, wherein the combination of three or more genes comprises MMP3 and SAA4 (constitutive SAA).
6. The method of claim 4 wherein the combination of three or more genes comprises YKL-40 and CCL18.
7. The method of claim 4, comprising measuring the expression level of CXCL13.
8. The method of claim 4, comprising measuring the expression level of MMP3.
9. The method of claim 4, comprising measuring the expression level of SAA4 (constitutive SAA).
10. The method of claim 4, wherein the patient is on immunomodulatory therapy.
11. The method of any one of claims 1-10, wherein the biological sample is selected from lung tissue, serum, and plasma.
12. Use of an IPF therapeutic agent in the manufacture of a medicament for the treatment of an IPF patient previously determined to have a prognosis of shortened survival according to the method of any one of claims 1-11.
13. The use of claim 12, wherein the IPF therapeutic agent is selected from an anti-IL-13 agent, an anti-IL-4 agent, a combination anti-IL-13/anti-IL-4 agent, pirfenidone, anti-LOXL2 antibody, N-acetylcysteine, anti-TGF- β antibody, anti- α v β 6 integrin antibody, anti-CTGF antibody, anti-

CCL2 antibody, somatostatin analog, angiotensin II inhibitor, carbon monoxide, thalidomide, tetrathiomolybdate, doxycycline, minocycline, and tyrosine kinase inhibitor.

14. The use of claim 13, wherein:

- a) the anti-LOXL2 antibody is GS-6624;
- b) the anti-TGF- β antibody is GC1008;
- c) the anti- α v β 6 integrin antibody is STX-100;
- d) the anti-CTGF antibody is FG-3019;
- e) the anti-CCL2 antibody is CNTO 888;
- f) the somatostatin analog is SOM230 or octreotide;
- g) the angiotensin II inhibitor is losartan; or
- h) the tyrosine kinase inhibitor is BIBF1120.

15. The use of claim 13, wherein the anti-IL-13 agent is lebrikizumab.

16. The use of claim 13, wherein the anti-IL-13 agent is an anti-IL-13 antibody comprising three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6.

17. The use of claim 16, wherein the anti-IL-13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9.

18. The use of claim 17, wherein the anti-IL-13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14.

19. The use of any one of claims 15-18, wherein the anti-IL-13 antibody is to be administered subcutaneously once every four weeks at a flat dose selected from 125 mg, 250 mg, and 500 mg.

20. The use of claim 19, wherein the anti-IL-13 antibody is to be administered subcutaneously once every four weeks at a flat dose of 250 mg.

21. The use of any one of claims 12-20, wherein the treatment extends the time to disease progression compared to no treatment, wherein disease progression is indicated by the first occurrence of one or more of the following: (i) death; (ii) non-elective hospitalization; (iii) 10% or greater decrease from baseline in FVC.

22. The use of claim 21, wherein disease progression is further indicated by decrease from baseline of $\geq 15\%$ in DL_{CO} at week 52.

23. The use of any one of claims 12-20, wherein a decrease in DL_{CO} from baseline 52 weeks after treatment is less than 15%.
24. The use of any one of claims 12-20, wherein the treatment results in less reduction in decline from baseline in distance walked by the patient in a 6-minute walk test 52 weeks after treatment compared to no treatment.
25. The use of claim 24, wherein the reduction in decline from baseline in distance walked is greater than 50 meters, or greater than 30 meters, or greater than 10 meters.
26. The use of any one of claims 12-20, wherein the treatment extends the time to a first event of acute IPF exacerbation or a first event of IPF deterioration compared to no treatment.
27. A method of monitoring disease progression in an IPF patient comprising, measuring in biological samples obtained from the patient at a first time point and one or more additional time points the expression of a combination of three or more genes, or expression of a combination of three or more proteins encoded by the combination of three or more genes, wherein the combination of three or more genes is selected from COMP, MMP3, YKL-40, CXCL13, SAA4 (constitutive SAA) and SPP1 (OPN), wherein the combination of three or more genes comprises MMP3, wherein a change in expression level from the first time point to the one or more additional time points is indicative of disease progression.
28. The method of claim 27, wherein the combination of three or more genes comprises YKL-40.
29. The method of claim 27, wherein the combination of three or more genes further comprises MMP7.
30. The method of claim 27, wherein the combination of three or more genes further comprises a gene selected from CCL11, CCL13, CCL17, and CCL18.
31. The method of any one of claims 27-30, wherein the biological samples are selected from lung tissue, serum, and plasma.
32. The method of claim 31, wherein the biological sample is lung tissue or plasma and the expression of the one or the combination of genes is measured using a PCR method or a microarray chip.
33. The method of claim 31, wherein the biological sample is serum and the expression of the one or the combination of proteins is measured using an immunoassay.
34. The method of any one of claims 27-33, wherein the patient is to be further treated with a candidate therapeutic agent in a clinical study.
35. The method of claim 34, wherein the candidate therapeutic agent is selected from an anti-IL-13 agent, an anti-IL-4 agent, a combination anti-IL-13/anti-IL-4 agent, pirfenidone, anti-

LOXL2 antibody, N-acetylcysteine, anti-TGF- β antibody, anti- α v β 6 integrin antibody, anti-CTGF antibody, anti-CCL2 antibody, somatostatin analog, angiotensin II inhibitor, carbon monoxide, thalidomide, tetrathiomolybdate, doxycycline, minocycline, and tyrosine kinase inhibitor.

36. The method of claim 35, wherein:

- a) the anti-LOXL2 antibody is GS-6624;
- b) the anti-TGF- β antibody is GC1008;
- c) the anti- α v β 6 integrin antibody is STX-100;
- d) the anti-CTGF antibody is FG-3019;
- e) the anti-CCL2 antibody is CNTO 888;
- f) the somatostatin analog is SOM230 or octreotide;
- g) the angiotensin II inhibitor is losartan; or
- h) the tyrosine kinase inhibitor is BIBF1120.

37. The method of claim 35, wherein the anti-IL-13 agent is lebrikizumab.

38. The method of claim 35, wherein the anti-IL-13 agent is an anti-IL-13 antibody comprising three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6.

39. The method of claim 38, wherein the anti-IL-13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9.

40. The method of claim 39, wherein the anti-IL-13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14.