

addition, compositions and methods of the disclosure are based, at least in part, on the identification of serum or blood biomarkers that are prognostic for survival of IPF patients. Such biomarkers are particularly useful for identifying and selecting IPF patients for therapeutic treatment according to the methods of the disclosure. The terms “molecular phenotype” and “molecular subtype” are used interchangeably herein.

[0015a] In a first aspect, there is provided 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.

[0016] Accordingly, in one embodiment, methods of prognosing or of aiding prognosis of idiopathic pulmonary fibrosis (IPF) are provided. In certain embodiments, a biological sample is obtained from the patient and the 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 is measured. In certain embodiments, an elevated expression level of the one or the combination of genes or elevated expression of the one or the combination of proteins encoded by the one or the combination of genes, is indicative of a prognosis for shortened survival compared to median survival. In certain embodiments, reduced expression of the one or the combination of genes or reduced expression of the one or the combination of proteins encoded by the one or the combination of genes, is indicative of a prognosis for increased survival compared to median survival. In one embodiment, the one or the combination of genes is selected from any of Table 2, Table 3, Table 4, or Table 5. In one embodiment, the one or the combination of genes is selected from MUCL1, MUC4, MUC20, PRR7, PRR15, SPRR1B, SPRR2D, KRT5, KRT6B, KRT13, KRT14, KRT15, KRT17, SERPINB3, SERPINB4, SERPINB5, SERPINB13, CLCA2, TRPV4, BBS5, MMP3, and SAA4. In one embodiment, the one or the combination of genes is selected from CXCR3, CXCR5, CXCL13, CCR6, CCR7, CD19, MS4A1 (CD20), 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@, IGHA1, IGKV2-

[0029a] In one aspect, there is provided 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.

[0030] In still yet another embodiment, methods of monitoring disease progression in an IPF patient are provided. In certain embodiments, the methods comprise obtaining a biological sample from the patient at a first time point and one or more additional time points, measuring in the biological samples the 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, wherein the one or the combination of genes is selected from any of Table 2, Table 3, Table 4, or Table 5, wherein a change in expression level from the first time point to the one or more additional time points is indicative of disease progression. In one embodiment, the one or the combination of genes, or the one or the combination of proteins, is selected from MUCL1, MUC4, MUC20, PRR7, PRR15, SPRR1B, SPRR2D, KRT5, KRT6B, KRT13, KRT14, KRT15, KRT17, SERPINB3, SERPINB4, SERPINB5, SERPINB13, CLCA2, TRPV4, BBS5, MMP3, and SAA4. In one embodiment, the one or the combination of genes is selected from CXCR3, CXCR5, CXCL13, CCR6, CCR7, CD19, MS4A1 (CD20), 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@, IGHA1, IGKV2-24, IGKV1D-8, IGHM. In one embodiment, the one or the combination of genes, or the one or the combination of proteins, 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. In one embodiment, the one or the combination of genes, or the one or the combination of proteins is selected from CHI3L1 (YKL-40), CCL11, CCL13, CCL17, CCL18, COMP, CXCL13, MMP3, MMP7, SAA4 (constitutive SAA), POSTN, AND SPP1 (OPN). In certain embodiments, a biological sample is selected from lung tissue, serum, and plasma. 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

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 MMP3.
- ~~32.~~ The method of claim 1, wherein the combination of three or more genes comprises YKL-40.
- ~~43.~~ The method of claim 1, wherein the combination of three or more genes further comprises MMP7.
- ~~54.~~ The method of claim 1, wherein the combination of three or more genes further comprises a gene selected from CCL11, CCL13, CCL17, and CCL18.
- ~~65.~~ The method of claim 1, wherein the combination of three or more genes comprises MMP3 and SAA4 (constitutive SAA).
- ~~76.~~ The method of claim ~~54~~ wherein the combination of three or more genes comprises YKL-40 and CCL18.
- ~~87.~~ The method of claim ~~54~~, comprising measuring the expression level of CXCL13.
- ~~98.~~ The method of claim ~~54~~, comprising measuring the expression level of MMP3.
- ~~109.~~ The method of claim ~~54~~, comprising measuring the expression level of SAA4 (constitutive SAA).
- ~~110.~~ The method of claim ~~54~~, wherein the patient is on immunomodulatory therapy.
- ~~1211.~~ The method of any one of claims 1-~~110~~, wherein the biological sample is selected from lung tissue, serum, and plasma.
- ~~1312.~~ 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.

~~14~~13. The method of claim ~~13~~12, wherein the total baseline biomarker score of the patient is two or above and the patient is selected for treatment with a candidate therapeutic agent in a clinical study, 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 (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).

~~15~~14. The method of claim ~~14~~13, wherein the anti-IL-13 agent is lebrikizumab.

~~16~~15. The method of claim ~~14~~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~~16. The method of claim ~~16~~15, 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~~17. The method of claim ~~17~~16, 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~~18. The method of claim ~~14~~13, wherein the anti-IL-13/anti-IL-4 agent is a bispecific antibody.

~~20~~19. 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.

2120. The method of any one of claims ~~13-20~~12-19, wherein the biological sample is selected from serum and plasma.

2221. The method of claim ~~20~~19, wherein the total baseline biomarker score of the patient is one or above and the patient is selected for treatment with a candidate therapeutic agent in a clinical study, 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 (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).

2322. The method of claim 2221, wherein the anti-IL-13 agent is lebrikizumab.

2423. The method of claim 2221, wherein the anti-IL-13/anti-IL-4 agent is a bispecific antibody.

2524. The method of claim 2221, 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.

2625. The method of claim 2524, 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.
2726. The method of claim 2625, 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.
2827. 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 ~~1-13~~12, 2019, or 2120.
2928. The use of claim 2827, 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 (GS-6624), N-acetylcysteine, anti-TGF- β antibody (GC1008), anti- $\alpha v \beta 6$ 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).
3029. The use of claim 2928, wherein the anti-IL-13 agent is lebrikizumab.
3130. The use of claim ~~29-28~~, 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.
3231. The use of claim 3130, 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.
3332. The use of claim 3231, 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.
3433. The use of any one of claims ~~30-33~~29-32, 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.
3534. The use of claim 3433, wherein the anti-IL-13 antibody is to be administered subcutaneously once every four weeks at a flat dose of 250 mg.

~~36~~35. Use of an IPF therapeutic agent in the manufacture of a medicament for the treatment of an IPF patient, provided that the patient has a baseline score of two or above determined according to the method of claim ~~13~~12.

~~37~~36. Use of an IPF therapeutic agent in the manufacture of a medicament for the treatment of an IPF patient, provided that the patient has a baseline score of one or above determined according to the method of claim ~~20~~19.

~~38~~37. The use of claim ~~36-35~~ or claim ~~37~~36, 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 (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).

~~39~~38. The use of claim ~~38~~37, wherein the anti-IL-13 agent is lebrikizumab.

~~40~~39. The use of claim ~~38~~37, 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.

~~41~~40. The use of claim ~~40~~39, 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.

~~42~~41. The use of claim ~~41~~40, 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.

~~43~~42. The use of any one of claims ~~39~~38-41, 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.

~~44~~43. The use of claim ~~43~~42, wherein the anti-IL-13 antibody is to be administered subcutaneously once every four weeks at a flat dose of 250 mg.

~~45~~44. The use of claim ~~38~~37, wherein the IPF therapeutic agent is a combination anti-IL-13/anti-IL-4 agent.

~~46~~45. The use of claim ~~45~~44, wherein the anti-IL-13/anti-IL-4 agent is a bispecific antibody.

~~4746~~. The use of any one of claims ~~28-4627-45~~, 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.

~~4847~~. The use of claim ~~4746~~, wherein disease progression is further indicated by decrease from baseline of $\geq 15\%$ in DL_{CO} at week 52.

~~4948~~. The use of any one of claims ~~28-4627-45~~, wherein a decrease in DL_{CO} from baseline 52 weeks after treatment is less than 15%.

~~5049~~. The use of any one of claims ~~28-4627-45~~, 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.

~~5150~~. The use of claim ~~5049~~, 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.

~~5251~~. The use of any one of claims ~~28-4627-45~~, 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.

~~5352~~. 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.

~~54. The method of claim 53, wherein the combination of three or more genes comprises MMP3.~~

~~5553~~. The method of claim ~~5352~~, wherein the combination of three or more genes comprises YKL-40.

~~5654~~. The method of claim ~~5352~~, wherein the combination of three or more genes further comprises MMP7.

~~5755~~. The method of claim ~~5352~~, wherein the combination of three or more genes further comprises a gene selected from CCL11, CCL13, CCL17, and CCL18.

~~5856~~. The method of any one of claims ~~53-5752-55~~, wherein the biological samples are selected from lung tissue, serum, and plasma.

~~5957~~. The method of claim ~~5856~~, 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.

~~60~~58. The method of claim ~~58~~56, wherein the biological sample is serum and the expression of the one or the combination of proteins is measured using an immunoassay.

~~61~~59. The method of any one of claims ~~53-60~~52-58, wherein the patient is to be further treated with a candidate therapeutic agent in a clinical study.

~~62~~60. The method of claim ~~61~~59, 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 (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).

~~63~~61. The method of claim ~~62~~60, wherein the anti-IL-13 agent is lebrikizumab.

~~64~~62. The method of claim ~~62~~60, 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.

~~65~~63. The method of claim ~~64~~62, 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.

~~66~~64. The method of claim ~~65~~63, 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.