many links between IL-13, IL-4 and asthma in the literature, many IL13 and/or IL4 antagonists therapies have had disappointing results in the clinic. Currently, no IL-13 or IL-4 antagonist therapy has been approved for use in asthma. Furthermore, moderate to severe asthmatic patients continue to lack good, alternative treatment options. Thus, there is a need to identify better therapies for treating asthma and improved methods for understanding how to treat asthma patients.

[0006] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety for any purpose.

SUMMARY

[0007] This application provides therapeutic agents for inhibiting the TH2 pathway and better methods of using the same. This application also provides better methods for diagnosing disease for use in treating the disease optionally with the TH2 pathway inhibitor.

[0008] The methods of treatment and diagnosis as provided herein can be applied to patients suffering from asthma, eosinophilic disorder, respiratory disorders, IL-13 mediated disorder and/or IgE-mediated disorder, or symptoms related to those disorders. Patients suffering from asthma-like symptoms, include patients that have not been diagnosed with asthma may be treated according to the methods provided herein.

[0009] According to one embodiment, a patient treated according to the methods provided herein suffers from asthma, an eosinophilic disorder, a respiratory disorder, an IL-13 mediated disorder and/or an IgE-mediated disorder, or symptoms related to those disorders, and does not have cancer or a neoplasm. According to another embodiment, the patient treated according to the methods provided herein is suffering from asthma, eosinophilic disorder, respiratory disorders, IL-13 mediated disorder and/or IgE-mediated disorder, or symptoms related to those disorders, and is 12 years old or older, 18 years old or older or 19 years old or older, or between 12-17 years old or between 18-75 years old.

[0010] In one embodiment, a patient treated with a TH2 pathway inhibitor according to this ~~invention~~disclosure is also treated with one, two, three or more therapeutic agents. In one embodiment, the patient is an asthma patient. According to one embodiment, the patient is treated with the TH2 pathway inhibitor and one, two, three or more therapeutic agents, wherein at least one therapeutic agent, other than the TH2 inhibitor, is a corticosteroid, a leukotriene antagonist, a LABA, a corticosteroid/LABA combination composition, a theophylline, cromolyn sodium, nedocromil sodium, omalizumab, a LAMA, a MABA, a 5-

Lipoxygenase Activating Protein (FLAP) inhibitor, or an enzyme PDE-4 inhibitor.

According to one ~~aspect of the invention~~embodiment, a TH2 pathway inhibitor is administered to an asthma patient diagnosed as EIP status, wherein the diagnosis comprises the use of an EID assay (alone or in combination with other assays) to determine the EIP status. In one further embodiment, the asthma patient is uncontrolled on a corticosteroid prior to the treatment. In another embodiment, the asthma patient is also being treated with a second controller. In one embodiment, the second controller is a corticosteroid, a LABA or a leukotriene antagonist. In a further embodiment, the asthma patient is suffering from moderate to severe asthma. Thus, in one embodiment, the patient to be treated with the TH2 pathway inhibitor is a moderate to severe asthma patient who is uncontrolled on a corticosteroid prior to treatment with the TH2 pathway inhibitor, and then is treated with the TH2 pathway inhibitor and one, two, three or more controllers. In one embodiment, at least one of the controllers is a corticosteroid. In a further embodiment, such patient is treated with a TH2 pathway inhibitor, a corticosteroid and another controller. In another embodiment, the patient is suffering from mild asthma but is not being treated with a corticosteroid. It should be understood that the therapeutic agents may have different treatment cycles as compared with the TH2 inhibitor and, consequently can be administered at different times compared to the TH2 inhibitor as a part of the patient's treatment. Therefore, according to one embodiment, a method of treatment according to this ~~invention~~disclosure comprises the steps of administering to a patient a TH2 pathway inhibitory and optionally, administering at least one, two or three additional therapeutic agents. In one embodiment, the TH2 pathway inhibitor is present in a composition with another therapeutic agent. In another embodiment, the TH2 pathway inhibitor is not present in a composition with another therapeutic agent.

[0011] According to another embodiment, the ~~invention~~disclosure comprises a method for treating asthma comprising administering an anti-IL-13 antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10 or an anti-IL13 antibody comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 as a flat dose. In one embodiment an anti-IL13 antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10 is administered as a 125-1000 mg flat dose (i.e., not weight dependent), by subcutaneous injection or by intravenous injection, at a frequency of time selected from: every 2 weeks, every 3 weeks, and every 4 weeks. In one embodiment an anti-IL13 antibody comprising

HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 is administered as a 125-1000 mg flat dose (i.e., not weight dependent), by subcutaneous injection or by intravenous injection, at a frequency of time selected from: every 2 weeks, every 3 weeks, and every 4 weeks. In one embodiment, the anti-IL13 antibody is lebrikizumab, which is administered as a 125-1000 mg flat dose (i.e., not weight dependent), by subcutaneous injection or by intravenous injection, at a frequency of time selected from: every 2 weeks, every 3 weeks, and every 4 weeks. In another embodiment, the patient is diagnosed with EIP status using a Total Periostin Assay to determine EIP status.

[0012] According to another embodiment, an antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10 is administered to treat asthma in a therapeutically effective amount sufficient to reduce the rate of exacerbations of the patient over time or improve FEV1. In yet another embodiment, the ~~invention~~disclosure comprises a method for treating asthma comprising administering an anti-IL-13 antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10 or an anti-IL13 antibody comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 as a flat dose (i.e., not weight dependent) of 37.5 mg, or a flat dose of 125 mg, or a flat dose of 250 mg. In certain embodiments, the dose is administered by subcutaneous injection once every 4 weeks for a period of time. In certain embodiments, the period of time is 6 months, one year, two years, five years, ten years, 15 years, 20 years, or the lifetime of the patient. In certain embodiments, the asthma is severe asthma and the patient is inadequately controlled or uncontrolled on inhaled corticosteroids plus a second controller medication. In another embodiment, the patient is diagnosed with EIP status using a Total Periostin Assay to determine EIP status and the patient is selected for treatment with an anti-IL13 antibody as described above. In another embodiment, the method comprises treating an asthma patient with an anti-IL13 antibody as described above where the patient was previously diagnosed with EIP status using a Total Periostin Assay to determine EIP status. In one embodiment, the asthma patient is age 18 or older. In one embodiment, the asthma patient is age 12 to 17 and the anti-IL13 is administered in as a flat dose of 250 mg or a flat dose of 125 mg. In one embodiment, the

asthma patient is age 6 to 11 and the anti-IL13 antibody is administered in as a flat dose of 125 mg or a flat dose of 62.5 mg.

[0013] The present ~~invention~~disclosure provides a periostin assay. In one embodiment, the periostin assay is a Total Periostin Assay. In another embodiment, the Total Periostin Assay comprises the use of one or more of the anti-periostin antibodies of this ~~invention~~disclosure to bind to the Total Periostin in a biological sample obtained from a patient. In yet another embodiment of this ~~invention~~disclosure, the biological sample is serum obtained from whole blood. In one embodiment, the biological sample is obtained from an asthma patient. In a further embodiment, the asthma patient is a moderate to severe asthma patient. In yet a further embodiment the moderate to severe asthma patient is uncontrolled on a corticosteroid and optionally, is being treated with one, two, three or more controllers.

[0014] The anti-periostin assays and antibody assays disclosed herein can be used for other diseases in which periostin is elevated such as idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), and cancer.

[0015] The present ~~invention~~disclosure provides a therapeutic agent that is a TH2 pathway inhibitor for use in treating asthma or a respiratory disorder in a patient, wherein the patient expresses elevated levels of total periostin. In one embodiment, the target for inhibition in the TH2 pathway is selected from: IL-9, IL-5, IL-13, IL-4, OX40L, TSLP, IL-25, IL-33 and IgE; and receptors such as: IL-9 receptor, IL-5 receptor, IL-4receptor alpha, IL-13receptoralpha1 and IL-13receptoralpha2, OX40, TSLP-R, IL-7Ralpha (a co-receptor for TSLP), IL17RB (receptor for IL-25), ST2 (receptor for IL-33), CCR3, CCR4, CRTH2, FcepsilonRI and FcepsilonRII/CD23 (receptors for IgE). In one embodiment, the patient to be treated according to the methods of the present ~~invention~~disclosure is suffering from mild to severe asthma, optionally moderate to severe asthma, and whose asthma is uncontrolled on a corticosteroid. In a further embodiment, the serum level of Total Periostin in the moderate to severe asthmatic patient who is uncontrolled on a corticosteroid is greater than 20ng/ml, 21 ng/ml, 22 ng/ml, 23 ng/ml, 24ng/ml or 25ng/ml in a E4 Assay. In yet a further embodiment, the patient to be treated additionally has elevated expression levels of any one, combination or all CEA, TARC (CCL17) and MCP-4 (CCL13)mRNAs or proteins. In yet a further embodiment, the patient to be treated in addition to having elevated expression levels of periostin as described herein, has a FE_{NO} level greater than 21 ppb, or greater than 35 ppb.

[0016] The present ~~invention~~disclosure provides the use of a therapeutic agent that binds a TH2 induced asthma pathway target in the preparation of a medicament for the treatment of a

patient having asthma or a respiratory disorder, wherein the patient expresses elevated levels of total periostin, and wherein the target is IL-9, IL-5, IL-13, IL-4, OX40L, TSLP, IL-25, IL-33 and IgE; and receptors such as: IL-9 receptor, IL-5 receptor, IL-4receptor alpha, IL-13receptoralpha1 and IL-13receptoralpha2, OX40, TSLP-R, IL-7Ralpha (a co-receptor for TSLP), IL17RB (receptor for IL-25), ST2 (receptor for IL-33), CCR3, CCR4, CRTH2, FcepsilonRI or FcepsilonRII/CD23 (receptors for IgE). In one embodiment, the patient is EIP. According to one embodiment, the patient was determined to have EIP by using an assay according to this ~~invention~~disclosure. In yet another embodiment, the assay is a Total Periostin Assay. In another embodiment, the assay measures the level of Total Periostin in a biological sample obtained from the patient. In one embodiment, the assay measures the level of Total Periostin protein in the serum sample obtained from the patient.

[0017] The present ~~invention~~disclosure comprises a kit or article for manufacture for diagnosing an asthma subtype in a patient comprising:

[0018] (1) determining the levels of Total Periostin in a serum sample obtained from the patient and optionally the protein expressions levels for one or more proteins selected from TARC and MCP-4; and

[0019] (2) instructions for measuring the expression levels of the Total Periostin and optionally the TARC and/or MCP-4 proteins in the serum sample, wherein the elevated expression levels of any one, combination or all of said proteins is indicative of the asthma subtype.

[0020] In yet another embodiment, methods of identifying an asthma patient or a respiratory disorder patient who is likely to be responsive to treatment with a TH2 Pathway Inhibitor are provided. In certain embodiments, the methods comprise determining whether the patient is Eosinophilic Inflammation Positive (EIP) using an Eosinophilic Inflammation Diagnostic Assay (EIDA), wherein the EIP status indicates that the patient is likely to be responsive to treatment with a TH2 Pathway Inhibitor.

[0021] In another embodiment, methods of identifying an asthma patient or a respiratory disorder patient who is likely to suffer from severe exacerbations are provided. In certain embodiments, the methods comprise determining whether the patient is EIP using an EIDA, wherein the EIP status indicates that the patient is likely to suffer from an increase in severe exacerbations.

[0022] In yet still another embodiment, methods of identifying an asthma patient or a respiratory disorder patient who is less likely to be responsive to treatment with a TH2

Pathway Inhibitor are provided. In certain embodiments, the methods comprise determining whether the patient is Eosinophilic Inflammation Negative (EIN) using an EIDA, wherein the EIN status indicates that the patient is less likely to be responsive to treatment with the TH2 Pathway Inhibitor.

[0023] In another embodiment, methods of monitoring an asthma patient being treated with a TH2 Pathway inhibitor are provided. In certain embodiments, the methods comprise determining whether the patient is EIP or EIN using an EIDA. In one embodiment, the method comprises determining a treatment regimen for the TH2 Pathway Inhibitor. In one embodiment, the determination of EIP indicates continuing therapy with the TH2 Pathway Inhibitor and the determination of EIN indicates discontinuing therapy with the TH2 Pathway Inhibitor.

[0024] In certain embodiments, the EIDA used in methods described above comprises the steps of: (a) determining the amount of Total Periostin in a sample obtained from an asthma patient; (b) comparing the amount of Total Periostin determined in step (a) to a reference amount; and (c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step (b).

[0024a] Therefore, in one aspect, there is provided a method of identifying an asthma patient or a respiratory disorder patient who is likely to be responsive to treatment with a TH2 Pathway Inhibitor comprising determining whether the patient is Eosinophilic Inflammation Positive (EIP) using an Eosinophilic Inflammation Diagnostic Assay (EIDA), wherein the EIP status indicates that the patient is likely to be responsive to treatment with the TH2 Pathway Inhibitor, wherein the EIDA comprises the steps of:

a) determining the amount of Total Periostin in a sample obtained from said patient;

b) comparing the amount of Total Periostin determined in step a) to a reference amount; and

c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step b).

[0024b] In another aspect, there is provided a method of identifying an asthma patient or a respiratory disorder patient who is likely to suffer from severe exacerbations comprising determining whether the patient is Eosinophilic Inflammation Positive (EIP) using an Eosinophilic Inflammation Diagnostic Assay (EIDA), wherein the EIP status indicates that the patient is likely to suffer from an increase in severe exacerbations, wherein the EIDA comprises the steps of:

a) determining the amount of Total Periostin in a sample obtained from said patient;

b) comparing the amount of Total Periostin determined in step a) to a reference amount; and

c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step b).

[0024c] In yet another aspect, there is provided a method of identifying an asthma patient or a respiratory disorder patient who is less likely to be responsive to treatment with a TH2 Pathway Inhibitor comprising determining whether the patient is Eosinophilic Inflammation Negative (EIN) using an Eosinophilic Inflammation Diagnostic Assay (EIDA), wherein the EIN status indicates that the patient is less likely to be responsive to treatment with the TH2 Pathway Inhibitor, wherein the EIDA comprises the steps of:

a) determining the amount of Total Periostin in a sample obtained from said patient;

b) comparing the amount of Total Periostin determined in step a) to a reference amount; and

c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step b).

[0024d] In yet a further aspect, there is provided a method of monitoring an asthma patient being treated with a TH2 Pathway inhibitor, comprising determining whether the patient is Eosinophilic Inflammation Positive (EIP) or Eosinophilic Inflammation Negative (EIN) using an Eosinophilic Inflammation Diagnostic Assay (EIDA), wherein the EIDA comprises the steps of:

a) determining the amount of Total Periostin in a sample obtained from said patient;

b) comparing the amount of Total Periostin determined in step a) to a reference amount; and

c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step b).

[0024e] In certain embodiments, the Total Periostin is serum periostin, which periostin is a measured using an immunoassay. In certain embodiments, the immunoassay is a sandwich immunoassay. In certain embodiments, the sandwich immunoassay is performed by an Elecsys® analyzer (Roche Diagnostics GmbH). In certain embodiments, the sandwich immunoassay is an E4 Assay. In one embodiment, the reference amount for EIP is 23 ng/ml greater when using the E4 Assay in step (a). In one embodiment,

the reference amount for EIP is 50 ng/ml or greater when using the Elecsys® analyzer in step (a). In one embodiment, the reference amount for EIN is 21 ng/ml or lower when using the E4 Assay in step (a). In one embodiment, the reference amount for EIN is 48 ng/ml or lower when using the Elecsys® analyzer in step (a).

[0025] In certain embodiments, the patient according to the methods described above is suffering from moderate to severe asthma. In certain embodiments, the asthma or respiratory disorder is uncontrolled on a corticosteroid. In certain embodiments, the corticosteroid is an inhaled corticosteroid. In certain embodiments, the inhaled corticosteroid is Qvar®, Pulmicort®, Symbicort®, Aerobid®, Flovent®, Flonase®, Advair® or Azmacort®. In one embodiment, the patient is also being treated with a second controller. In certain embodiments, the second controller is a long acting bronchial dilator (LABD). In certain embodiments, the LABD is a long-acting beta-2 agonist (LABA), leukotriene receptor

H3 is residues 97-106 of SEQ ID NO:24, [ARDNWDAMDY]; (d) the HVR-L1 is residues 24-39 of SEQ ID NO:25, [RSSQSLVHNNANTYLH]; (e) the HVR-L2 is residues 55-61 of SEQ ID NO:25, [KVSNRFS]; (f) the HVR-L3 is residues 94-102 of SEQ ID NO:25 [SQNTLVPWT].

[0027] In another aspect, there is provided uses of a kit for detecting Total Periostin in a biological sample that has been obtained from an asthma patient for stratifying/classifying asthma patients into likely responders and non-responders for therapeutic treatment with a TH2 Pathway Inhibitor. In certain embodiments, the Total Periostin is detected using an EIDA, which EIDA comprises the steps of: (a) determining the amount of Total Periostin in a sample obtained from an asthma patient; (b) comparing the amount of Total Periostin determined in step (a) to a reference amount; and (c) stratifying said patient into the category of responder or non-responder based on the comparison obtained in step (b). In certain embodiments, the Total Periostin is serum periostin, which periostin is a measured using an immunoassay. In certain embodiments, the immunoassay is a sandwich immunoassay. In certain embodiments, the sandwich immunoassay is performed by an Elecsys® analyzer (Roche Diagnostics GmbH). In certain embodiments, the sandwich immunoassay is an E4 Assay. In one embodiment, the reference amount for EIP is 23 ng/ml greater when using the E4 Assay in step (a). In one embodiment, the reference amount for EIP is 50 ng/ml or greater when using the Elecsys® analyzer in step (a).

[0028] In certain embodiments, the patient according to the uses described in the paragraph above is suffering from moderate to severe asthma. In certain embodiments, the asthma or respiratory disorder is uncontrolled on a corticosteroid. In certain embodiments, the corticosteroid is an inhaled corticosteroid. In certain embodiments, the inhaled corticosteroid is Qvar®, Pulmicort®, Symbicort®, Aerobid®, Flovent®, Flonase®, Advair® or Azmacort®. In one embodiment, the patient is also being treated with a second controller. In certain embodiments, the second controller is a long acting bronchial dilator (LABD). In certain embodiments, the LABD is a long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline, or oral corticosteroids (OCS). In certain embodiments, the LABD is Symbicort®, Advair®, Brovana®, Foradil®, Perforomist™ or Serevent®.

[0029] In certain embodiments, the TH2 Pathway Inhibitor according to the uses above inhibits the target ITK, BTK , IL-9 (e.g., MEDI-528), IL-5 (e.g., Mepolizumab, CAS No. 196078-29-2; resilizumab), IL-13 (e.g., IMA-026, IMA-638 (also referred to as,

anrukinzumab, INN No. 910649-32-0; QAX-576; IL4/IL13 trap), tralokinumab (also referred to as CAT-354, CAS No. 1044515-88-9); AER-001, ABT-308 (also referred to as humanized 13C5.5 antibody), IL-4 (e.g., AER-001, IL4/IL13 trap), OX40L, TSLP, IL-25, IL-33 and IgE (e.g., XOLAIR, QGE-031; MEDI-4212); and receptors such as: IL-9 receptor, IL-5 receptor (e.g., MEDI-563 (benralizumab, CAS No. 1044511-01-4), IL-4receptor alpha (e.g., AMG-317, AIR-645), IL-13receptoralpha1 (e.g., R-1671) and IL-13receptoralpha2, OX40, TSLP-R, IL-7Ralpha (a co-receptor for TSLP), IL17RB (receptor for IL-25), ST2 (receptor for IL-33), CCR3, CCR4, CRTH2 (e.g., AMG-853, AP768, AP-761, MLN6095, ACT129968), FcepsilonRI, FcepsilonRII/CD23 (receptors for IgE), Flap (e.g., GSK2190915), Syk kinase (R-343, PF3526299); CCR4 (AMG-761), TLR9 (QAX-935), or is a multi-cytokine inhibitor of CCR3, IL5, IL3, GM-CSF (e.g., TPI ASM8). In certain embodiments, the TH2 Pathway Inhibitor is an anti-IL13/IL4 pathway inhibitor or an anti IgE binding agent. In certain embodiments, the TH2 Pathway Inhibitor is an anti- anti-IL-13 antibody. In certain embodiments, the anti-IL-13 antibody is an antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10, an anti-IL13 antibody comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 or lebrikizumab. In certain embodiments, the anti-IL-13 antibody is a bispecific antibody that also binds IL-4. In certain embodiments, the TH2 Pathway Inhibitor is an anti-IgE antibody. In certain embodiments, the anti-IgE antibody is (i) the XOLAIR® antibody, (ii) anti-M1' antibody comprising a variable heavy chain and a variable light chain, wherein the variable heavy chain is SEQ ID NO:24 and the variable light chain is SEQ ID NO:25 or (iii) an anti- M1' antibody comprising a variable heavy chain and a variable light chain, wherein the variable heavy chain further comprises an HVR-H1, HVR-H2 and HVR-H3, and the variable light chain further comprises and HVR-L1, HVR, L2 and HVR-L3 and: (a) the HVR-H1 is residues 26-35 of SEQ ID NO:24, [GFTFSDYGIA]; (b) the HVR-H2 is residues 49-66 of SEQ ID NO:24, [AFISDLAYTIYYADTVTG]; (c) the HVR-H3 is residues 97-106 of SEQ ID NO:24, [ARDNWDAMDY]; (d) the HVR-L1 is residues 24-39 of SEQ ID NO:25, [RSSQSLVHNNANTYLH]; (e) the HVR-L2 is residues 55-61 of SEQ ID NO:25, [KVSNRFS]; (f) the HVR-L3 is residues 94-102 of SEQ ID NO:25 [SQNTLVPWT].

[0030] In yet another aspect, there is provided a kits for measuring the Total Periostin in a biological sample obtained from an asthma patient or a patient suffering from a respiratory disorder, ~~are~~

~~provided,~~ wherein the kit comprises ~~either (1)~~ a first nucleic acid molecule that hybridizes to a second nucleic acid molecule, wherein the second nucleic acid molecule encodes Total Periostin or a portion thereof, or ~~(2)~~ the kit comprises an antibody that binds to Total Periostin. In certain embodiments, the kit comprises a package insert containing information describing the uses provided above.

[0031] In still yet another aspect, ~~there is provided a~~ kit~~s~~ for diagnosing an asthma subtype in a patient ~~are provided, the kits~~ comprising: (1) determining the levels of Total Periostin in a serum sample obtained from the patient and ~~optionally~~ the protein expressions levels in the serum sample for one or more proteins selected from TARC and MCP-4; and (2) instructions for measuring the ~~expression~~ levels of the Total Periostin and ~~one or more proteins selected from~~ ~~optionally~~ TARC and ~~/or~~ MCP-4 in the serum sample, wherein the elevated expression levels of any one, combination or all of said proteins is indicative of the asthma subtype. In certain embodiments, the kit further comprises a package insert for determining whether an asthma patient or respiratory disorder patient is EIP or EIN. In certain embodiments, the kit further comprises a package insert for determining whether an asthma patient is likely to respond to a TH2 Pathway Inhibitor. In certain embodiments, the kit further comprises a package insert containing information describing any of the uses provided above. In certain embodiments, the kit further comprises an empty container to hold a biological sample. In certain embodiments, the kit comprises two anti-periostin antibodies for use in an immunoassay for determining Total Periostin levels.

[0032] In another ~~aspect~~embodiment, methods of treating an asthma or a respiratory disorder comprising administering an anti-IL-13 antibody comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 to a patient suffering from asthma or a respiratory disorder in a 125-500mg flat dose every 2-8 weeks. In certain embodiments, the patient is suffering from moderate to severe asthma. In certain embodiments, the asthma or respiratory disorder is uncontrolled on a corticosteroid. In certain embodiments, the asthma or respiratory disorder is uncontrolled on an inhaled corticosteroid. In certain embodiments, the asthma or respiratory disorder is uncontrolled on a total daily dose of at least 500 mcg fluticasone propionate (FP). In certain embodiments, the corticosteroid is an inhaled corticosteroid is Qvar®, Pulmicort®, Symbicort®, Aerobid®, Flovent®, Flonase®, Advair®, Azmacort®. In certain embodiments, the patient is being treated with a second controller. In certain embodiments, the patient is continuing to be treated with a corticosteroid, optionally an inhaled

corticosteroid, during the treatment with the anti-IL13 antibody. In certain embodiments, the patient is continuing to be treated with a second controller during the treatment with the anti-IL-13 antibody. In certain embodiments, the second controller is a long acting bronchial dilator. In certain embodiments, the long acting bronchial dilator is a LABA, LTRA, LAMA, theophylline, or OCS. In certain embodiments, the patient has been determined to be EIP. In certain embodiments, the patient has been determined to be EIP using a kit a described above. In certain embodiments, the patient has been determined to be EIP using a method as described above. In certain embodiments, the patient is administered a flat dose of 125 mg or 250mg every four weeks. In certain embodiments, the patient is 18 years or older, or the patient is 12-17 years old or 12 years old and older, or the patient is 6-11 years old or 6 years old and older.

[0033] In certain embodiments, the anti-IL-13 antibody is administered subcutaneously. In certain embodiments, the anti-IL-13 antibody is administered using a prefilled syringe or autoinjector device. In certain embodiments, the asthma patient to be treated according to the methods above is 18 years old or older and has serum periostin at $\geq$ 50 ng/mL and is uncontrolled on an inhaled corticosteroid and a second controller medication. In certain embodiments, the serum periostin is measured using an immunoassay, which immunoassay is selected from Elecsys® periostin assay and E4 Assay. In certain embodiments, the serum periostin is measured using a kit as described above. In certain embodiments, the anti-IL-13 antibody is an antibody comprising a VH comprising SEQ ID NO:9 and a VL comprising SEQ ID NO:10. In certain embodiments, the anti-IL-13 antibody is lebrikizumab. In certain embodiments, the asthma patient to be treated according to the methods described above is 12 years old and above and uncontrolled on an inhaled corticosteroid and a second controller medication.

[0034] In yet another ~~aspect~~embodiment, methods of treating asthma or a respiratory disease comprising administering a therapeutically effective amount of lebrikizumab to the patient are provided. In certain embodiments, the treatment results in a relative improvement in FEV1 of greater than 5% compared to before treatment with lebrikizumab. In certain embodiments, the relative improvement in FEV1 is greater than 8% compared to before treatment with lebrikizumab. In certain embodiments, the treatment results in a reduction in severe exacerbations.

[0035] In still another ~~aspect~~embodiment, methods of treating of a patient suffering from asthma or a respiratory disease comprising administering a TH2 Pathway Inhibitor to the patient

13C5.5 antibody), IL-4 (e.g., AER-001, IL4/IL13 trap), OX40L, TSLP, IL-25, IL-33 and IgE (e.g., XOLAIR®, QGE-031; MEDI-4212); and receptors such as: IL-9 receptor, IL-5 receptor (e.g., MEDI-563 (benralizumab, CAS No. 1044511-01-4), IL-4receptor alpha (e.g., AMG-317, AIR-645), IL-13receptoralpha1 (e.g., R-1671) and IL-13receptoralpha2, OX40, TSLP-R, IL-7Ralpha (a co-receptor for TSLP), IL17RB (receptor for IL-25), ST2 (receptor for IL-33), CCR3, CCR4, CRTH2 (e.g., AMG-853, AP768, AP-761, MLN6095, ACT129968), FcepsilonRI, FcepsilonRII/CD23 (receptors for IgE), Flap (e.g., GSK2190915), Syk kinase (R-343, PF3526299); CCR4 (AMG-761), TLR9 (QAX-935), or is a multi-cytokine inhibitor of CCR3, IL5, IL3, GM-CSF (e.g., TPI ASM8). In certain embodiments, the TH2 Pathway Inhibitor is an anti-IL13/IL4 pathway inhibitor or an anti IgE binding agent. In certain embodiments, the TH2 Pathway Inhibitor is an anti- anti-IL-13 antibody. In certain embodiments, the anti-IL-13 antibody is an antibody comprising a VH comprising SEQ ID NO:9 and VL comprising SEQ ID NO:10, an anti-IL13 antibody comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, and HVRL3, the respective HVRs having the amino acid sequence of SEQ ID NO.: 11, SEQ ID NO.: 12, SEQ ID NO.: 13, SEQ ID NO.: 14, SEQ ID NO.: 15, and SEQ ID NO.: 16 or lebrikizumab. In certain embodiments, the anti-IL-13 antibody is a bispecific antibody that also binds IL-4.

[0039] In certain embodiments, the TH2 Pathway Inhibitor is an anti-IgE antibody. In certain embodiments, the anti-IgE antibody is (i) the XOLAIR® antibody, (ii) anti-M1' antibody comprising a variable heavy chain and a variable light chain, wherein the variable heavy chain is SEQ ID NO:24 and the variable light chain is SEQ ID NO:25 or (iii) an anti-M1' antibody comprising a variable heavy chain and a variable light chain, wherein the variable heavy chain further comprises an HVR-H1, HVR-H2 and HVR-H3, and the variable light chain further comprises and HVR-L1, HVR, L2 and HVR-L3 and: (a) the HVR-H1 is residues 26-35 of SEQ ID NO:24, [GFTFSDYGIA]; (b) the HVR-H2 is residues 49-66 of SEQ ID NO:24, [AFISDLAYTIYYADTVTG]; (c) the HVR-H3 is residues 97-106 of SEQ ID NO:24, [ARDNWDAMDY]; (d) the HVR-L1 is residues 24-39 of SEQ ID NO:25, [RSSQSLVHNNANTYLH]; (e) the HVR-L2 is residues 55-61 of SEQ ID NO:25, [KVSNRFS]; (f) the HVR-L3 is residues 94-102 of SEQ ID NO:25 [SQNTLVPWT].

[0040] In another ~~aspect~~embodiment, methods for evaluating adverse events in a patient associated with treatment of asthma with lebrikizumab are provided. In certain embodiments, the methods comprise the steps of monitoring the number and/or severity of events that are exacerbations, community-acquired pneumonia, anaphylaxis, musculoskeletal pains,

musculoskeletal disorders, connective tissue pains or connective tissue disorders. In certain embodiments, the musculoskeletal or connective tissue disorder is arthralgia, back pain, pain in extremity, myalgia, neck pain, arthritis, bone development abnormalities, bursitis, costochondritis, exostosis, flank pain, musculoskeletal chest pain, musculoskeletal pain, pain in jaw or tendinitis.

[0041] In yet another ~~aspect~~embodiment, anti-periostin antibodies are provided. In certain embodiments, the anti-periostin antibody comprises the HVR sequences of SEQ ID NO:1 and the HVR sequences of SEQ ID NO:2. In certain embodiments, the anti-periostin antibody comprises the sequences of SEQ ID NO:1 and SEQ ID NO:2. In certain embodiments, the anti-periostin antibody comprises the HVR sequences of SEQ ID NO:3 and the HVR sequences of SEQ ID NO:4. In certain embodiments, the anti-periostin antibody comprises the sequences of SEQ ID NO:3 and SEQ ID NO:4. In certain embodiments, Total Periostin Assays comprising the use of the above anti-periostin antibodies are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] Figure 1 provides a schematic of the allergen challenge trial described in Example 1.

[0043] Figure 2 shows allergen-induced changes in FEV1 following challenges in screening (A) and at week 13 (B). FEV1 was measured every 10 minutes for the first 90minutes and then every hour from 2-8 hours following allergen challenge. Error bars represent standard errors of the mean.

[0044] Figure 3 shows serum levels of IgE, CCL13 (MCP-4), and CCL17 (TARC). (A) Serum levels expressed as % predose levels over time in placebo-treated patients and (B) lebrikizumab-treated patients. Lines represent individual patients; groups medians not indicated. Arrows indicated dosing at weeks 0, 4, 8, and 12 (days 0, 28, 56 and 84). (C) Reductions in IgE, CCL13, and CCL17 at Week 13 in individual patients relative to baseline levels of those markers.

[0045] Figure 4 shows lebrikizumab-induced inhibition of the late asthmatic response (LAR) in biomarker-high and biomarker-low patient subgroups. Data are expressed as placebo-corrected mean reduction in AUC (area under the curve) of the LAR at Week 13 (n=5 to 8 active patients/group).

[0046] Figure 5 provides is a schematic of an asthma trial described in Example 2.