

such associations could be utilized as an integral component in efforts to identify specific subsets of UC or CD patients, such as TNF-IR patients, who would be expected to significantly benefit from treatment with anti-beta7 integrin subunit antibodies, for example where the therapeutic agent is or has been shown in clinical studies to be of therapeutic benefit in such specific UC or CD patient subpopulation.

[0017] The invention described herein meets certain of the above-described needs and provides other benefits.

[0018] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety for any purpose.

SUMMARY

[0019] The methods of the ~~invention~~disclosure are based, at least in part, on the discovery that mRNA expression levels of certain genes in intestinal biopsies and in peripheral whole blood, as well as cellular protein expression levels of certain genes in intestinal biopsies are predictive of responsiveness of patients suffering from a gastrointestinal inflammatory disorder to treatment with integrin beta7 antagonists.

[0020] In one aspect, the present invention refers to a method of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder to a therapy comprising an integrin beta7 antagonist, the method comprising measuring the level of mRNA expression of at least one gene in a biological sample obtained from the patient, wherein the gene is selected from integrin beta7, integrin alphaE, and CD3epsilon, comparing the mRNA expression level detected in the sample to a reference level, and predicting that the patient will respond to the therapy when the level of mRNA expression has been measured as elevated compared to the reference level and predicting that the patient will not respond to the therapy when the level of mRNA expression has been measured as low compared to the reference level. Accordingly, in one aspect~~example~~, methods of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder to a therapy comprising an integrin beta7 antagonist are ~~provided~~disclosed. In certain ~~embodiments~~examples, a biological sample is obtained from the patient and levels of mRNA expression are measured. In one ~~embodiment~~example, expression of integrin beta7 mRNA is measured. In one ~~embodiment~~example, expression of integrin alphaE mRNA is measured. In one ~~embodiment~~example, expression of CD3epsilon is measured. In one ~~embodiment~~example, expression of a combination of two or three mRNAs selected from integrin beta7, integrin alphaE, and CD3epsilon is measured. In one ~~embodiment~~example, the biological sample is a tissue biopsy sample. In one ~~embodiment~~example, the biopsy is obtained from intestinal tissue.

In one ~~embodiment~~example, the biological sample is peripheral whole blood. In one ~~embodiment~~example, the peripheral whole blood is collected in a PAXgene tube. In certain ~~example~~embodiments, the mRNA expression level is measured by a PCR method. In one ~~example~~embodiment, the PCR method is qPCR. In certain ~~examples~~embodiments, the mRNA expression level is compared to a median value. In one ~~example~~embodiment, the patient is predicted to respond to therapy comprising the integrin beta7 antagonist if the mRNA expression level of one or more of integrin beta7, integrin alphaE, or CD3epsilon is elevated compared to a reference value, which in certain ~~embodiments~~examples is a median value. In one ~~example~~embodiment, the patient is predicted to not respond to therapy comprising the integrin beta7 antagonist if the mRNA

expression level of one or more of integrin beta7, integrin alphaE, or CD3epsilon is low compared to a reference value, which in certain ~~embodiments~~examples, is a median value. In one ~~exampleembodiment~~, the response is clinical remission. In one ~~exampleembodiment~~, the response is mucosal healing. In one ~~exampleembodiment~~, the response is clinical response. In certain ~~examplesembodiments~~, remission in the patient is determined to be induced when the absolute Mayo Clinic Score ≤ 2 and no individual subscore >1 , which is also referred to as clinical remission. In certain ~~examplesembodiments~~, mucosal healing is determined to have occurred when the patient is determined to have an endoscopy subscore of 0 or 1 as assessed by flexible sigmoidoscopy. In certain such ~~examplesembodiments~~, patients who experience mucosal healing are determined to have an endoscopy subscore of 0.

[0021] In another aspect, the present invention refers to a method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising determining the mRNA expression level of at least one gene selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient, wherein elevated mRNA expression level compared to a reference level identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment. In another example, methods of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment are ~~provided~~disclosed. In one ~~embodiment~~example, the mRNA expression level of integrin beta7 in a biological sample from the patient is determined. In one ~~embodiment~~example, the mRNA expression level of integrin alphaE in a biological sample from the patient is determined. In one ~~exampleembodiment~~, the mRNA expression level of CD3epsilon in a biological sample from the patient is determined. In one ~~exampleembodiment~~, the mRNA expression level of two or three mRNAs selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample from the patient is determined. In certain ~~examplesembodiments~~, elevated integrin beta7 mRNA expression compared to a reference value, for example, a median value, or elevated integrin alphaE mRNA expression compared to a reference value, for example, a median value, or elevated CD3epsilon mRNA expression compared to a reference value, for example, a median value, detected in the biological sample identifies the patient as one who is likely to respond to integrin beta7 antagonist treatment.

[0022] In yet another ~~example~~aspect, a biological sample is obtained from the patient and the number of cells expressing one or a combination of certain proteins are measured and compared to the total number of cells or the number of protein-expressing cells is determined in a high power field under a light microscope. In one ~~exampleembodiment~~, the number of integrin beta7-expressing cells is measured. In one ~~exampleembodiment~~, the number of integrin alphaE-

expressing cells is measured. In one exampleembodiment, the number of CD3epsilon-expressing cells is measured. In one exampleembodiment, the number of cells expressing a combination of two or three proteins selected from integrin beta7, integrin alphaE, and CD3epsilon is measured. In one exampleembodiment, the biological sample is a tissue biopsy sample. In one exampleembodiment, the biopsy is obtained from intestinal tissue. In one exampleembodiment, the biological sample is placed into formalin and optionally embedded in paraffin blocks. In certain exampleembodiments, the

number of cells expressing one or a combination of integrin beta7, integrin alphaE, or CD3epsilon is measured by an immunohistochemical method. In certain exampleembodiments, the number of cells expressing one or a combination of integrin beta7, integrin alphaE, or CD3epsilon is compared to the total number of cells in a given area. In one exampleembodiment, the patient is predicted to respond to therapy comprising the integrin beta7 antagonist if the number of cells expressing one or more of integrin beta7, integrin alphaE, or CD3epsilon is elevated (or high) compared to a reference value, for example, a median value. In one exampleembodiment, the patient is predicted to not respond to therapy comprising the integrin beta7 antagonist if the number of cells expressing one or more of integrin beta7, integrin alphaE, or CD3epsilon is low compared to a reference value, for example, a median value. In one exampleembodiment, the response is clinical remission. In one exampleembodiment, the response is mucosal healing. In one exampleembodiment, the response is clinical response. In certain exampleembodiments, remission in the patient is determined to be induced when the absolute Mayo Clinic Score ≤ 2 and no individual subscore >1 , which is also referred to as clinical remission. In certain exampleembodiments, mucosal healing is determined to have occurred when the patient is determined to have an endoscopy subscore of 0 or 1 as assessed by flexible sigmoidoscopy. In certain such exampleembodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0.

[0023] In still another aspect, the present invention refers to a method of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist, the method comprising (a) measuring the level of mRNA expression of at least one gene in a biological sample obtained from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the level of mRNA expression measured in (a) to a reference level; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level. In another example, methods of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist are provideddisclosed. In certain embodimentsexamples, the methods comprise: (a) measuring the level of mRNA expression of at least one gene in a biological sample from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the level of mRNA expression measured in (a) to a reference level; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level. In

one ~~example~~~~embodiment~~, the patient is a human. In one ~~example~~~~embodiment~~, the patient is a TNF inadequate responder (TNF-IR). In one ~~example~~~~embodiment~~, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission.

[0024] In a further aspect, the present invention refers to use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, the use comprising (a) measuring the level of mRNA expression of at least one gene in a biological sample obtained from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the level of mRNA expression measured in (a) to a reference level; (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level; and (d) the use of the medicament when the level of mRNA expression measured in (a) is above the reference level. In another example, methods of treating a patient having a gastrointestinal inflammatory disorder are ~~provided~~disclosed. In certain ~~embodiments~~examples, the methods comprise: (a)

measuring the level of mRNA expression of at least one gene in a biological sample from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the level of mRNA expression measured in (a) to a reference level; (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level; and (d) administering the therapy when the level of mRNA expression measured in (a) is above the reference level, thereby treating the gastrointestinal inflammatory disorder. In one embodimentexample, 100 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one embodimentexample, a flat loading dose of 420 mg of the integrin beta7 antagonist is administered subcutaneously, followed two weeks after administration of the loading dose by a second subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed two weeks after the second administration by a third subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed four weeks after the third administration by subcutaneous administration of 300 mg of the integrin beta7 antagonist and thereafter subcutaneous administration of 300 mg of the integrin beta7 antagonist once every four weeks. In one embodimentexample, the patient is a human. In one exampleembodiment, the patient is a TNF inadequate responder (TNF-IR). In one exampleembodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one exampleembodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one exampleembodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In one exampleembodiment, administration of the integrin beta7 antagonist results in one or more of the following: (1) a 3-point decrease and 30% reduction from baseline in MCS and ≥ 1 -point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1, (2) an endoscopic subscore of 0 or 1, (3) MCS ≤ 2 with no individual subscore > 1 .

[0025] In still yet another aspect, the present invention refers to a method of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder to a therapy comprising an integrin beta7 antagonist, the method comprising measuring the number of cells expressing at least one protein selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient, comparing the number of expressing cells measured in the sample to a reference level, and predicting that the patient will respond to the therapy when the number of protein-expressing cells has been measured as elevated compared to the reference level and predicting that the patient will not respond to the therapy when the number of protein-expressing cells has been measured as low compared to the reference level. In another example, methods of predicting the response of a patient suffering from a gastrointestinal

inflammatory disorder to a therapy comprising an integrin beta7 antagonist are provideddisclosed. In certain ~~embodiment~~examples, the methods comprise: obtaining a biological sample from the patient, measuring the number of cells expressing at least one protein selected from integrin beta7, integrin alphaE, and CD3epsilon, comparing the number of expressing cells measured in the sample to a reference level, and predicting the response of the patient to the therapy, wherein elevated numbers of expressing cells compared to the reference level indicates response to the therapy and a low number of expressing cells compared to the reference level indicates non-response to the therapy. In one ~~embodiment~~example,

the patient is a human. In one ~~example~~~~embodiment~~, the patient is a TNF inadequate responder (TNF-IR). In one ~~example~~~~embodiment~~, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In one ~~example~~~~embodiment~~, the biological sample is intestinal tissue. In one ~~example~~~~embodiment~~, the methods comprise measuring the number of expressing cells by an immunohistochemical method. In one ~~example~~~~embodiment~~, the measuring comprises contacting the sample with an agent that specifically binds to integrin beta7 protein, integrin alphaE protein, or CD3epsilon protein and detecting the amount of complex formed, and thereby measuring the number of expressing cells. In one ~~example~~~~embodiment~~, the number of expressing cells in the sample is divided by the total number of cells in the sample. In one ~~embodiment~~~~example~~, the number of expressing cells in a high power field under a light microscope is determined. In one ~~example~~~~embodiment~~, the reference level is a median value.

[0026] In another aspect, the present invention refers to a method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising determining the number of cells expressing at least one protein selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient, wherein elevated numbers of expressing cells compared to a reference level identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment. In one example, methods of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment are ~~provided~~disclosed. In certain ~~embodiments~~examples, the methods comprise determining the number of cells expressing at least one protein selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample from the patient, wherein elevated numbers of expressing cells compared to a reference level identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment. In one ~~example~~~~embodiment~~, the patient is a human. In one ~~example~~~~embodiment~~, the patient is a TNF inadequate responder (TNF-IR). In one ~~embodiment~~~~example~~, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In one ~~example~~~~embodiment~~, the biological sample is intestinal tissue. In one ~~example~~~~embodiment~~, the methods comprise measuring the number of expressing cells by an immunohistochemical method. In one ~~example~~~~embodiment~~, the measuring comprises contacting

the sample with an agent that specifically binds to integrin beta7 protein, integrin alphaE protein, or CD3epsilon protein and detecting the amount of complex formed, and thereby measuring the number of expressing cells. In one exampleembodiment, the number of expressing cells in the sample is divided by the total number of cells in the sample. In one exampleembodiment, the number of expressing cells in a high power field under a light microscope is determined. In one exampleembodiment, the reference level is a median value.

[0027] In yet another aspect, the present invention refers to a method of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist, the method comprising (a) measuring the number of cells expressing at least one protein in a biological sample obtained from the patient, wherein the at least one protein is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the number of cells measured in (a) to a reference level; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the number of cells measured in (a) is above the reference level. In another example, methods of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist are ~~provided~~disclosed. In certain ~~embodiment~~examples, the methods comprise: (a) measuring the number of cells expressing at least one protein in a biological sample from the patient, wherein the at least one protein is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the number of cells measured in (a) to a reference level; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the number of cells measured in (a) is above the reference level. In one ~~embodiment~~example, the patient is a human. In one ~~example~~embodiment, the patient is a TNF inadequate responder (TNF-IR). In one ~~example~~embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one ~~example~~embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one ~~example~~embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In one ~~example~~embodiment, the biological sample is intestinal tissue. In one ~~example~~embodiment, the methods comprise measuring the number of expressing cells by an immunohistochemical method. In one ~~example~~embodiment, the measuring comprises contacting the sample with an agent that specifically binds to integrin beta7 protein, integrin alphaE protein, or CD3epsilon protein and detecting the amount of complex formed, and thereby measuring the number of expressing cells. In one ~~example~~embodiment, the number of expressing cells in the sample is divided by the total number of cells in the sample. In one ~~embodiment~~example, the number of expressing cells in a high power field under a ^{11a} microscope is determined. In one ~~example~~embodiment, the reference level is a median value.

[0028] In yet still another aspect, the present invention refers to use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, the use comprising (a) measuring the number of cells expressing at least one protein in a biological sample obtained from the patient, wherein the at least one protein is

selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the number of expressing cells measured in (a) to a reference level; (c) identifying the patient as more likely to respond to a therapy comprising an integrin beta7 antagonist when the number of protein-expressing cells measured in (a) is above the reference level; and (d) the use of the medicament when the number of protein-expressing cells measured in (a) is above the reference level. In another example, methods of treating a patient having a gastrointestinal inflammatory disorder are provideddisclosed. In certain embodimentsexamples, the method comprise: (a) measuring the number of cells expressing at least one protein in a biological sample from the patient, wherein the at least one protein is selected from integrin beta7, integrin alphaE, and CD3epsilon; (b) comparing the number of expressing cells measured in (a) to a reference level; (c) identifying the patient as more likely to respond to a therapy comprising an integrin beta7 antagonist when the number of expressing cells measured in (a) is above the reference level; and (d) administering the therapy when the number of expressing cells measured in (a) is above the reference level, thereby treating the gastrointestinal inflammatory disorder. In one embodimentexample, 100 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one exampleembodiment, a flat loading dose of 420 mg of the integrin beta7 antagonist is administered subcutaneously, followed two weeks after administration of

the loading dose by a second subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed two weeks after the second administration by a third subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed four weeks after the third administration by subcutaneous administration of 300 mg of the integrin beta7 antagonist and thereafter subcutaneous administration of 300 mg of the integrin beta7 antagonist once every four weeks. In one ~~example~~~~embodiment~~, the patient is a human. In one ~~example~~~~embodiment~~, the patient is a TNF inadequate responder (TNF-IR). In one ~~example~~~~embodiment~~, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one ~~example~~~~embodiment~~, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In one ~~example~~~~embodiment~~, administration of the integrin beta7 antagonist results in one or more of the following: (1) a 3-point decrease and 30% reduction from baseline in MCS and ≥ 1 -point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1, (2) an endoscopic subscore of 0 or 1, (3) MCS ≤ 2 with no individual subscore > 1 . In one ~~example~~~~embodiment~~, the biological sample is intestinal tissue. In one ~~example~~~~embodiment~~, the methods comprise measuring the number of expressing cells by an immunohistochemical method. In one ~~example~~~~embodiment~~, the measuring comprises contacting the sample with an agent that specifically binds to integrin beta7 protein, integrin alphaE protein, or CD3epsilon protein and detecting the amount of complex formed, and thereby measuring the number of expressing cells. In one ~~example~~~~embodiment~~, the number of expressing cells in the sample is divided by the total number of cells in the sample. In one ~~example~~~~embodiment~~, the number of expressing cells in a high power field under a light microscope is determined. In one ~~example~~~~embodiment~~, the reference level is a median value.

[0029] In still yet another ~~aspect~~~~example~~, an integrin beta7 antagonist for use in treating a patient having a gastrointestinal inflammatory disorder is ~~provided~~~~disclosed~~. In certain ~~embodiments~~~~examples~~, the patient is treated or selected for treatment when the level of mRNA expression of at least one gene selected from integrin beta7, integrin alphaE, and CD3epsilon is above a reference level. In certain ~~examples~~~~embodiments~~, the patient is treated or selected for treatment when the number of cells expressing at least on protein selected from integrin beta7, integrin alphaE, and CD3epsilon is elevated or high compared to a reference level. In one ~~embodiment~~~~example~~, the reference level is a median value. In one ~~example~~~~embodiment~~, the integrin beta7 antagonist is for use in treating the patient wherein 100 mg is administered subcutaneously once every four weeks. In one ~~example~~~~embodiment~~, the integrin beta7 antagonist is for use in treating the patient wherein a flat loading dose of 420 mg of the integrin beta7 antagonist is administered subcutaneously,

followed two weeks after administration of the loading dose by a second subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed two weeks after the second administration by a third subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed four weeks after the third administration by subcutaneous administration of 300 mg of the integrin beta7 antagonist and thereafter subcutaneous administration of 300 mg of the integrin beta7 antagonist once every four weeks.

[0030] In a further example aspect, in vitro use of at least one agent that specifically binds to a biomarker selected from integrin beta7 mRNA, integrin alphaE mRNA, CD3epsilon mRNA, integrin beta7 protein, integrin alphaE protein, and CD3epsilon protein is ~~provided~~disclosed. In certain example ~~embodiments~~, the at least one agent is used for identifying or selecting a patient having a gastroinflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist, wherein a level of integrin beta7, integrin alphaE, and/or CD3epsilon mRNA expression or a number of integrin beta7-, integrin alphaE-, and/or CD3epsilon-expressing cells above a reference level identifies or selects that the patient is more likely to respond to the therapy. In one example ~~embodiment~~, the reference level is a median value.

[0031] In still another example aspect, methods of treating a gastrointestinal inflammatory disorder in a patient are ~~provided~~disclosed. In certain example ~~embodiments~~, a therapeutically effective amount of an integrin beta7 antagonist is administered to a patient when a biological sample obtained from the patient has been determined to express elevated mRNA expression levels of one or more of certain genes. In one example ~~embodiment~~, the sample has been determined to express elevated integrin beta7 mRNA compared to the median value. In one example ~~embodiment~~, the sample has been determined to express elevated integrin alphaE mRNA compared to the median value. In one example ~~embodiment~~, the sample has been determined to express elevated CD3epsilon mRNA compared to the median value. In one example ~~embodiment~~, the sample has been determined to express elevated mRNA levels of two or three of integrin beta7, integrin alphaE, and CD3epsilon compared to the median levels of the same mRNAs. In certain example ~~embodiments~~, the patient has been selected for treatment based on elevated mRNA expression levels of certain genes in the biological sample compared to a median value of the same gene or genes. In one example ~~embodiment~~, the patient has been selected for treatment based on elevated integrin beta7 mRNA expression compared to the median value. In one example ~~embodiment~~, the patient has been selected for treatment based on elevated integrin alphaE mRNA expression compared to the median value. In one example ~~embodiment~~, the patient has been selected for treatment based on elevated CD3epsilon mRNA expression compared to the median value. In one ~~embodiment~~ example, the patient has been selected for treatment based on

elevated mRNA expression of two or three of integrin beta7, integrin alphaE, and CD3epsilon compared to the median values for the same mRNAs. In one exampleembodiment, the biological sample is a tissue biopsy sample. In one exampleembodiment, the biological sample is peripheral whole blood. In one exampleembodiment, the peripheral whole blood is collected in a PAXgene tube. In certain exampleembodiments, the mRNA expression level is measured by a PCR method. In one embodimentexample, the PCR method is qPCR. In certain exampleembodiments, administration of the integrin beta7 antagonist results in one or more of the following: (1) a 3-point decrease and 30% reduction from baseline in MCS and ≥ 1 -point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1, (2) an endoscopic subscore of 0 or 1, (3) $\text{MCS} \leq 2$ with no individual subscore > 1 . In one embodimentexample, 100 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one exampleembodiment, a flat loading dose of 420 mg of the integrin beta7 antagonist is administered subcutaneously, followed two weeks after administration of the loading dose by a second subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed two weeks after the second administration by a third subcutaneous administration of 300 mg of the integrin beta7 antagonist, followed four weeks after the third administration by subcutaneous administration of 300 mg of the integrin beta7 antagonist and thereafter subcutaneous administration of 300 mg of the integrin beta7 antagonist once every four weeks.

[0032] In certain of the above exampleembodiments, the gastrointestinal inflammatory disorder is an inflammatory bowel disease, and in certain such exampleembodiments, the inflammatory bowel disease is ulcerative colitis (UC) or Crohn's disease (CD), and in certain such embodimentexamples, the integrin beta7 antagonist is a monoclonal anti-beta7 antibody. In certain such exampleembodiments, the anti-beta7 antibody is selected from a chimeric antibody, a human antibody, and a humanized antibody. In certain exampleembodiments, the anti-beta7 antibody is an antibody fragment. In certain exampleembodiments, the anti-beta7 antibody comprises six hypervariable regions (HVRs), wherein:

(i) HVR-L1 comprises amino acid sequence A1-A11, wherein A1-A11 is RASESVDTYLH (SEQ ID NO:1); RASESVDSLH (SEQ ID NO:7), RASESVDTLLH (SEQ ID NO:8), or RASESVDDLH (SEQ ID NO:9) or a variant of SEQ ID NOs:1, 7, 8 or 9 (SEQ ID NO:26) wherein amino acid A2 is selected from the group consisting of A, G, S, T, and V and/or amino acid A3 is selected from the group consisting of S, G, I, K, N, P, Q, R, and T, and/or A4 is selected from the group consisting of E, V, Q, A, D, G, H, I, K, L, N, and R, and/or amino acid A5 is selected from the group consisting of S, Y, A, D, G, H, I, K, N, P, R, T, and V, and/or amino acid A6 is selected from the group consisting of V, R, I, A, G, K,

L, M, and Q, and/or amino acid A7 is selected from the group consisting of D, V, S, A, E, G, H, I, K, L, N, P, S, and T, and/or amino acid A8 is selected from the group consisting of D, G, N, E, T, P and S, and/or amino acid A9 is selected from the group consisting of L, Y, I and M, and/or amino acid A10 is selected from the group consisting of L, A, I, M, and V and/or amino acid A11 is selected from the group consisting of H, Y, F, and S;

(ii) HVR-L2 comprises amino acid sequence B1-B8, wherein B1-B8 is KYASQSSIS (SEQ ID NO:2), RYASQSSIS (SEQ ID NO:20), or XaaYASQSSIS (SEQ ID NO:21, where Xaa represents any amino acid) or a variant of SEQ ID NOs:2, 20 or 21 (SEQ ID NO:27) wherein amino acid B1 is selected from the group consisting of K, R, N, V, A, F, Q, H, P, I, L, Y and Xaa (where Xaa represents any amino acid), and/or amino acid B4 is selected from the group consisting of S and D, and/or amino acid B5 is selected from the group consisting of Q and S, and/or amino acid B6 is selected from the group consisting of S, D, L, and R, and/or amino acid B7 is selected from the group consisting of I, V, E, and K;

(iii) HVR-L3 comprises amino acid sequence C1-C9, wherein C1-C9 is QQGNLSPNT (SEQ ID NO:3) or a variant of SEQ ID NO:3 (SEQ ID NO:28) wherein amino acid C8 is selected from the group consisting of N, V, W, Y, R, S, T, A, F, H, I, L, and M;

(iv) HVR-H1 comprises amino acid sequence D1-D10 wherein D1-D10 is GFFITNNYWG (SEQ ID NO:4);

(v) HVR-H2 comprises amino acid sequence E1-E17 wherein E1-E17 is GYISYSGSTSYNPSLKS (SEQ ID NO:5), or a variant of SEQ ID NO:5 (SEQ ID NO:29) wherein amino acid E2 is selected from the group consisting of Y, F, V, and D, and/or amino acid E6 is selected from the group consisting of S and G, and/or amino acid E10 is selected from the group consisting of S and Y, and/or amino acid E12 is selected from the group consisting of N, T, A, and D, and/or amino acid 13 is selected from the group consisting of P, H, D, and A, and/or amino acid E15 is selected from the group consisting of L and V, and/or amino acid E17 is selected from the group consisting of S and G; and

(vi) HVR-H3 comprises amino acid sequence F2-F11 wherein F2-F11 is MTGSSGYFDF (SEQ ID NO:6) or RTGSSGYFDF (SEQ ID NO:19); or comprises amino acid sequence F1-F11, wherein F1-F11 is AMTGSSGYFDF (SEQ ID NO:16), ARTGSSGYFDF (SEQ ID NO:17), or AQTGSSGYFDF (SEQ ID NO:18), or a variant of SEQ ID NOs:6, 16, 17, 18, or 19 (SEQ ID NO:30) wherein amino acid F2 is R, M, A, E, G, Q, S, and/or amino acid F11 is selected from the group consisting of F and Y. In certain such examples, the anti-beta7 antibody comprises three heavy chain hypervariable region

(HVR-H1-H3) sequences and three light chain hypervariable region (HVR-L1-L3) sequences, wherein:

- (i) HVR-L1 comprises SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9;
- (ii) HVR-L2 comprises SEQ ID NO:2;
- (iii) HVR-L3 comprises SEQ ID NO:3;
- (iv) HVR-H1 comprises SEQ ID NO:4;
- (v) HVR-H2 comprises SEQ ID NO:5; and
- (vi) HVR-H3 comprises SEQ ID NO:6 or SEQ ID NO:16 or SEQ ID NO:17 or SEQ ID NO:19.

In certain example embodiments, the anti-beta7 antibody comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:24. In certain embodiments examples, the anti-beta7 antibody comprises a variable heavy chain comprising the amino acid sequence of SEQ ID NO:31 (SEQ ID NO:31 corresponds to SEQ ID NO:25 except that the amino acid sequence of HVR-H3 of SEQ ID NO:25 (MTGSSGYFDF (SEQ ID NO:6) or AMTGSSGYFDF (SEQ ID NO:16)) is substituted with RTGSSGYFDF (SEQ ID NO:19) or ARTGSSGYFDF (SEQ ID NO:17), respectively). In certain example embodiments, the anti-beta7 antibody comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:24 and a variable heavy chain comprising the amino acid sequence of SEQ ID NO:31. In certain example embodiments, the anti-beta7 antibody is rhuMAb Beta7, also referred to herein as etrolizumab.

[0033] In another example aspect, the integrin beta7 antagonist is a monoclonal anti-alpha4/beta7 antibody. In certain example embodiments, the anti-alpha4/beta7 antibody is vedolizumab. In certain example embodiments, the anti-alpha4/beta7 antibody is AMG 181.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Figure 1A and 1B shows alignment of sequences of the variable light and heavy chains for the following consensus sequences and anti-beta7 subunit antibody sequences: light chain human subgroup kappa I consensus sequence (FIG. 1A, SEQ ID NO:12), heavy chain human subgroup III consensus sequence (FIG. 1B, SEQ ID NO:13), rat anti-mouse beta7 antibody (Fib504) variable light chain (FIG. 1A, SEQ ID NO:10), rat anti-mouse beta7 antibody (Fib504) variable heavy chain (FIG. 1B, SEQ ID NO:11), and humanized antibody variants: Humanized hu504K graft variable light chain (FIG. 1A, SEQ ID NO:14), humanized hu504K graft variable heavy chain (FIG. 1B, SEQ ID NO:15), variants hu504-5, hu504-16, and hu504-32 (amino acid variations from humanized hu504K graft are indicated in FIG. 1A)

WHAT IS CLAIMED IS:

1. A method of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder to a therapy comprising an integrin beta7 antagonist, the method comprising:

~~obtaining a biological sample from the patient,~~
measuring the level of mRNA expression of at least one gene in ~~the a biological sample~~ obtained from the patient, wherein the gene is selected from integrin beta7, integrin alphaE, and CD3epsilon,
comparing the mRNA expression level detected in the sample to a reference level,
and

predicting that the patient will respond to the therapy when the level of mRNA expression has been measured as elevated compared to the reference level and predicting that the patient will not respond to the therapy when the level of mRNA expression has been measured as low compared to the reference level.

2. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising determining the mRNA expression level of at least one gene selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient, wherein elevated mRNA expression level compared to a reference level identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

3. A method of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist, the method comprising:

- (a) measuring the level of mRNA expression of at least one gene in a biological sample obtained from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon;
- (b) comparing the level of mRNA expression measured in (a) to a reference level; and
- (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level.

4. ~~A method of~~ Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, the method use comprising:

- (a) measuring the level of mRNA expression of at least one gene in a biological sample obtained from the patient, wherein the at least one gene is selected from integrin beta7, integrin alphaE, and CD3epsilon;
 - (b) comparing the level of mRNA expression measured in (a) to a reference level;
 - (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression measured in (a) is above the reference level; and
 - (d) ~~administering the therapy~~ the use of the medicament when the level of mRNA expression measured in (a) is above the reference level, ~~thereby treating the gastrointestinal inflammatory disorder.~~
5. The ~~method~~ use of claim 4, wherein 100 mg of the integrin beta7 antagonist is to be administered subcutaneously once every four weeks.
 6. The method of any one of claims 1-~~53~~ or the use of any one of claims 4-5, wherein the patient is a human.
 7. The method or use of claim 6, wherein the patient is a TNF inadequate responder (TNF-IR).
 8. The ~~method~~ use of claim ~~64~~, wherein the gastrointestinal inflammatory disorder is an inflammatory bowel disease.
 9. The ~~method~~ use of claim 8, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.
 10. The ~~method~~ use of claim 9, wherein the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission.
 11. The ~~method~~ use of claim ~~64~~, wherein the biological sample is selected from intestinal tissue and peripheral whole blood.
 12. The ~~method~~ use of claim ~~64~~, wherein the mRNA expression level is measured by a PCR method.
 13. The ~~method~~ use of claim 12, wherein the PCR method comprises qPCR.
 14. The ~~method~~ use of claim ~~64~~, wherein the measuring comprises amplifying one or more of integrin beta7 mRNA, integrin alphaE mRNA, or CD3epsilon mRNA and detecting the amplified mRNA, thereby measuring the level of amplified mRNA.
 15. The ~~method~~ use of claim ~~64~~, wherein the reference level is a median value.
 16. ~~A method of~~ Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a gastrointestinal inflammatory disorder in a patient, the method-use comprising administering to the patient is to be administered a therapeutically effective amount of an integrin beta7 antagonist, wherein

a biological sample obtained from the patient has been determined to express elevated mRNA expression levels of at least one gene selected from integrin beta7, integrin alphaE, and CD3epsilon

or

wherein the patient has been selected for treatment based on elevated mRNA expression levels in the biological sample obtained from the patient of at least one gene selected from integrin beta7, integrin alphaE, and CD3epsilon.

17. The ~~method~~use of claim 16, wherein 100 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks.

18. The ~~method~~use of claim 17, wherein the patient is a human.

19. The ~~method~~use of claim 18, wherein the patient is a TNF inadequate responder (TNF-IR).

20. The ~~method~~ of claim ~~18~~16, wherein the gastrointestinal inflammatory disorder is an inflammatory bowel disease.

21. The ~~method~~use of claim 20, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.

22. The ~~method~~use of claim ~~18~~16, wherein the biological sample is selected from biopsy and peripheral whole blood.

23. The ~~method~~use of claim 22, wherein the mRNA expression level is measured by a PCR method.

24. The ~~method~~use of claim 23, wherein the PCR method comprises qPCR.

25. A method of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder to a therapy comprising an integrin beta7 antagonist, the method comprising:

~~obtaining a biological sample from the patient;~~

measuring the number of cells expressing at least one protein selected from integrin

beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient,

comparing the number of expressing cells measured in the sample to a reference level,

and

predicting that the patient will respond to the therapy when the number of protein-expressing cells has been measured as elevated compared to the reference level and predicting that the patient will not respond to the therapy when the number of protein-expressing cells has been measured as low compared to the reference level.

26. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising determining the number of cells expressing at least one protein selected from integrin beta7, integrin alphaE, and CD3epsilon in a biological sample obtained from the patient, wherein elevated numbers of expressing cells compared to a reference level identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

27. A method of identifying a patient suffering from a gastrointestinal inflammatory disorder as likely to respond to a therapy comprising an integrin beta7 antagonist, the method comprising:

- (a) measuring the number of cells expressing at least one protein in a biological sample obtained from the patient, wherein the at least one protein is selected from integrin beta7, integrin alphaE, and CD3epsilon;
- (b) comparing the number of cells measured in (a) to a reference level; and
- (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the number of cells measured in (a) is above the reference level.

28. ~~A method of~~ Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, the method-use comprising:

- (a) measuring the number of cells expressing at least one protein in a biological sample obtained from the patient, wherein the at least one protein is selected from integrin beta7, integrin alphaE, and CD3epsilon;
- (b) comparing the number of expressing cells measured in (a) to a reference level;
- (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the number of protein-expressing cells measured in (a) is above the reference level; and
- (d) ~~administering the therapy~~ the use of the medicament when the number of protein-expressing cells measured in (a) is above the reference level, ~~thereby treating the gastrointestinal inflammatory disorder.~~

29. ~~The method-use~~ of claim 28, wherein 100 mg of the integrin beta7 antagonist is to be administered subcutaneously once every four weeks.

30. The method of any one of claims 25-27 or the use of any one of claims 28-29, wherein the patient is a human.

31. The method or use of claim 30, wherein the patient is a TNF inadequate responder (TNF-IR).

32. The method or use of claim 30, wherein the gastrointestinal inflammatory disorder is an inflammatory bowel disease.
33. The method or use of claim 32, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.
34. The method or use of claim 33, wherein the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission.
35. The ~~method~~use of claim ~~30~~28, wherein the biological sample is intestinal tissue.
36. The ~~method~~use of claim ~~30~~28, comprising measuring the number of expressing cells by an immunohistochemical method.
37. The ~~method~~use of claim ~~30~~28, wherein the measuring comprises contacting the sample with an agent that specifically binds to integrin beta7 protein, integrin alphaE protein, or CD3epsilon protein and detecting the amount of complex formed, and thereby measuring the number of protein-expressing cells.
38. The ~~method~~use of claim ~~30~~28, wherein the number of expressing cells in the sample is divided by the total number of cells in the sample.
39. The ~~method~~use of claim ~~30~~28, wherein the number of expressing cells in a high power field under a light microscope is determined.
40. The ~~method~~use of claim ~~30~~28, wherein the reference level is a median value.
41. The ~~method~~use of claim ~~10-5~~ or claim ~~34~~29, wherein ~~administration of the integrin beta7 antagonist~~ is to be administered results in one or more of the following: (1) a 3-point decrease and 30% reduction from baseline in MCS and ≥ 1 -point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1, (2) an endoscopic subscore of 0 or 1, (3) $MCS \leq 2$ with no individual subscore > 1 .
42. The method of any one of claims ~~1-3~~ or ~~25-27~~, or the use of any one of claims 4-24 or ~~28-41~~, wherein the integrin beta7 antagonist is a monoclonal anti-beta7 antibody.
43. The method or use of claim 42, wherein the anti-beta7 antibody is selected from a chimeric antibody, a human antibody, and a humanized antibody.
44. The method or use of claim 43, wherein the anti-beta7 antibody is an antibody fragment.
45. The method or use of claim 43, wherein the anti-beta7 antibody comprises six hypervariable regions (HVRs), wherein:
 - (i) HVR-L1 comprises amino acid sequence A1-A11, wherein A1-A11 is RASESVDTYLH (SEQ ID NO:1); RASESVDLLH (SEQ ID NO:7), RASESVDTLH (SEQ ID NO:8), or RASESVDLLH (SEQ ID NO:9) or a variant of SEQ ID NOs:1, 7, 8 or 9 (SEQ ID NO:26) wherein amino acid A2 is selected from the group consisting of A, G, S,

T, and V and/or amino acid A3 is selected from the group consisting of S, G, I, K, N, P, Q, R, and T, and/or A4 is selected from the group consisting of E, V, Q, A, D, G, H, I, K, L, N, and R, and/or amino acid A5 is selected from the group consisting of S, Y, A, D, G, H, I, K, N, P, R, T, and V, and/or amino acid A6 is selected from the group consisting of V, R, I, A, G, K, L, M, and Q, and/or amino acid A7 is selected from the group consisting of D, V, S, A, E, G, H, I, K, L, N, P, S, and T, and/or amino acid A8 is selected from the group consisting of D, G, N, E, T, P and S, and/or amino acid A9 is selected from the group consisting of L, Y, I and M, and/or amino acid A10 is selected from the group consisting of L, A, I, M, and V and/or amino acid A11 is selected from the group consisting of H, Y, F, and S;

(ii) HVR-L2 comprises amino acid sequence B1-B8, wherein B1-B8 is KYASQSSIS (SEQ ID NO:2), RYASQSSIS (SEQ ID NO:20), or XaaYASQSSIS (SEQ ID NO:21, where Xaa represents any amino acid) or a variant of SEQ ID NOs:2, 20 or 21 (SEQ ID NO:27) wherein amino acid B1 is selected from the group consisting of K, R, N, V, A, F, Q, H, P, I, L, Y and Xaa (where Xaa represents any amino acid), and/or amino acid B4 is selected from the group consisting of S and D, and/or amino acid B5 is selected from the group consisting of Q and S, and/or amino acid B6 is selected from the group consisting of S, D, L, and R, and/or amino acid B7 is selected from the group consisting of I, V, E, and K;

(iii) HVR-L3 comprises amino acid sequence C1-C9, wherein C1-C9 is QQGNSLPNT (SEQ ID NO:3) or a variant of SEQ ID NO:3 (SEQ ID NO:28) wherein amino acid C8 is selected from the group consisting of N, V, W, Y, R, S, T, A, F, H, I, L, and M;

(iv) HVR-H1 comprises amino acid sequence D1-D10 wherein D1-D10 is GFFITNNYWG (SEQ ID NO:4);

(v) HVR-H2 comprises amino acid sequence E1-E17 wherein E1-E17 is GYISYSGSTSYNPSLKS (SEQ ID NO:5), or a variant of SEQ ID NO:5 (SEQ ID NO:29) wherein amino acid E2 is selected from the group consisting of Y, F, V, and D, and/or amino acid E6 is selected from the group consisting of S and G, and/or amino acid E10 is selected from the group consisting of S and Y, and/or amino acid E12 is selected from the group consisting of N, T, A, and D, and/or amino acid 13 is selected from the group consisting of P, H, D, and A, and/or amino acid E15 is selected from the group consisting of L and V, and/or amino acid E17 is selected from the group consisting of S and G; and

(vi) HVR-H3 comprises amino acid sequence F2-F11 wherein F2 -F11 is MTGSSGYFDF (SEQ ID NO:6) or RTGSSGYFDF (SEQ ID NO:19); or comprises amino acid sequence F1-F11, wherein F1-F11 is AMTGSSGYFDF (SEQ ID NO:16),

ARTGSSGYFDF (SEQ ID NO:17), or AQTGSSGYFDF (SEQ ID NO:18), or a variant of SEQ ID NOs:6, 16, 17, 18, or 19 (SEQ ID NO:30) wherein amino acid F2 is R, M, A, E, G, Q, S, and/or amino acid F11 is selected from the group consisting of F and Y.

46. The method or use of claim 45, wherein the anti-beta7 antibody comprises three heavy chain hypervariable region (HVR-H1-H3) sequences and three light chain hypervariable region (HVR-L1-L3) sequences, wherein:

(i) HVR-L1 comprises SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9;

(ii) HVR-L2 comprises SEQ ID NO:2;

(iii) HVR-L3 comprises SEQ ID NO:3;

(iv) HVR-H1 comprises SEQ ID NO:4;

(v) HVR-H2 comprises SEQ ID NO:5; and

(vi) HVR-H3 comprises SEQ ID NO:6 or SEQ ID NO:16 or SEQ ID NO:17 or SEQ ID NO:19.

47. The method or use of claim 46, wherein the anti-beta7 antibody comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:24 and a variable heavy chain comprising the amino acid sequence of SEQ ID NO:31.

48. The method or use of claim 47, wherein the anti-beta7 antibody is etrolizumab.

49. The method of any one of claims 1-3 or 25-27, or the use of any one of claims 4-24 or 28-41, wherein the integrin beta7 antagonist is a monoclonal anti-alpha4/beta7 antibody.

50. The method or use of claim 49, wherein the anti-alpha4/beta7 antibody is selected from vedolizumab and AMG 181.