

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 biological samples obtained from patients, e.g., intestinal biopsies or blood, are predictive of responsiveness of patients suffering from a gastrointestinal inflammatory disorder to treatment with integrin beta7 antagonists.

[0020] Accordingly, ~~in one aspect,~~ disclosed are methods of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder, or predicting responsiveness of a gastrointestinal inflammatory disorder patient, to a therapy comprising an integrin beta7 antagonist ~~are provided.~~

[0020a] In one aspect, there is provided 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, at least two, at least three, or at least four High Expression Predictive Genes (“HEPG”) in a biological sample that has been obtained from the patient, selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3;

comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured; and

predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured has been measured as elevated compared to the respective reference level for each of the HEPG measured.

[0020b] In one aspect, there is provided a method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient, wherein elevated mRNA expression level of each of the HEPG measured compared to a reference level for each of the HEPG measured identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

[0020c] In certain embodiments, a biological sample is obtained from the patient and levels of mRNA expression are measured. In some embodiments, expression of at least one, at least two, at least three, or at least four High Expression Predictive Genes (“HEPG”) in the sample selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 are measured. In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1. In some embodiments, a further HEPG in addition to those identified above is measured, which further HEPG is ITGAE. In one embodiment, the biological sample is a tissue biopsy sample. In one embodiment, the biopsy is obtained from intestinal tissue. In certain such embodiments comprising a tissue biopsy sample or intestinal tissue, the HEPG does not include SLC8A3. In one embodiment, the biological sample is peripheral whole blood. In certain such embodiments comprising peripheral blood, the HEPG includes SLC8A3. In one embodiment, the peripheral whole blood is collected in a PAXgene tube. In certain embodiments, the mRNA expression level is measured by an RNA sequencing method, microarray or PCR method. In one embodiment, the PCR method is qPCR. In certain embodiments, the measuring comprises amplifying one or more of GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and

SLC8A3 mRNA, and optionally further comprises amplifying ITGAE mRNA, and detecting the amplified mRNA, thereby measuring the level of amplified mRNA. In certain embodiments, the mRNA expression level is compared to a reference level. In some embodiments, the mRNA expression level is compared to a reference level for each of the HEPG measured. In certain embodiments, each of the reference levels is a median value. In some embodiments, the patient is predicted to respond to therapy comprising the integrin beta7 antagonist when the mRNA expression level of at least one, at least two, at least three, or at least four HEPG in the sample selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 is elevated compared to a reference value for each of the HEPG measured, which in certain embodiments is a median value for each reference value. In one embodiment, the response is clinical remission. In one embodiment, the response is mucosal healing. In one embodiment, the response is clinical response. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0021] ~~In another aspect,~~ Also disclosed are 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. In certain embodiments~~ one aspect, there is provided 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 the methods comprise: (a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression measured in (a) to a reference level for each of the respective HEPG measured; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured. In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1,

FOXM1, SLC8A3, and ECH1. In some embodiments, a further HEPG in addition to those identified above is measured, which further HEPG is ITGAE. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0022] ~~In a further aspect, Further disclosed are~~ methods of treating a patient having a gastrointestinal inflammatory disorder ~~are provided~~. In certain embodiments, the methods comprise: (a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient; (b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the HEPG measured; (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured; and (d) administering the therapy when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured, thereby treating the gastrointestinal inflammatory disorder. In one aspect, there is provided use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising: (a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the HEPG measured; and (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured. In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1. In some embodiments, a further HEPG in addition to those identified above is measured, which further HEPG is ITGAE. In one embodiment, 105 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one embodiment, an initial dose of 210 mg of the integrin beta7 antagonist is administered

subcutaneously followed by subsequent doses, each subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously, administered at each of weeks 2, 4, 8 and 12 after the initial dose. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0023] ~~In yet another aspect,~~Disclosed are methods of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder, or predicting responsiveness of a gastrointestinal inflammatory disorder patient, to a therapy comprising an integrin beta7 antagonist ~~are provided~~ in which expression of at least one, at least two, or at least three Low Expression Predictive Genes ("LEPG") in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 are measured.

[0023a] In one aspect, there is provided 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, at least two, or at least three Low Expression Predictive Genes ("LEPG") in a biological sample that has been obtained from the patient, selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3,

comparing the mRNA expression level of each of the LEPG measured in the sample to a reference level for each of the LEPG measured, and predicting that the patient will respond to the therapy when the level of mRNA expression of each of the LEPG measured has been measured as reduced compared to the respective reference level for each of the LEPG measured.

[0023b] In one aspect, there is provided a method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient, wherein reduced mRNA expression level of each of the LEPG measured compared to a reference level for each of the LEPG measured identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

[0023c] In some embodiments, the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2. In some embodiments, at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15. In one embodiment, the biological sample is a tissue biopsy sample. In one embodiment, the biopsy is obtained from intestinal tissue. In certain such embodiments comprising a tissue biopsy sample or intestinal tissue, the LEPG includes SLC8A3. In one embodiment, the biological sample is peripheral whole blood. In certain such embodiments comprising peripheral blood, the LEPG does not include SLC8A3. In one embodiment, the peripheral whole blood is collected in a PAXgene tube. In certain embodiments, the mRNA expression level is measured by an RNA sequencing method,

microarray, or PCR method. In one embodiment, the PCR method is qPCR. In certain embodiments, the measuring comprises amplifying one or more of SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, VNN3 mRNA, and detecting the amplified mRNA, thereby measuring the level of amplified mRNA. In certain embodiments, the mRNA expression level is compared to a reference level. In some embodiments, the mRNA expression level is compared to a reference level for each of the LEPG measured. In certain embodiments, the reference level for each LEPG measured is a median value. In some embodiments, the patient is predicted to respond to therapy comprising the integrin beta7 antagonist when the mRNA expression level of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 are reduced compared to a reference value for each of the LEPG measured, which in certain embodiments is a median value for each reference value. In one embodiment, the response is clinical remission. In one embodiment, the response is mucosal healing. In one embodiment, the response is clinical response. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0024] ~~In still another aspect,~~Also disclosed are 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. In certain embodiments~~one aspect, there is provided 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 the methods comprise: (a) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression of each of the LEPG measured

in (a) to a reference level for each of the LEPG measured; and (c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each LEPG measured in (a) is below the respective reference level for each of the LEPG measured. In some embodiments, the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2. In some embodiments, at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0025] ~~In a further aspect,~~ Further disclosed are methods of treating a patient having a gastrointestinal inflammatory disorder are provided. In certain embodiments, the methods comprise: (a) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample from the patient; (b) comparing the level of mRNA expression of each LEPG measured in (a) to a reference level for each of the LEPG measured; (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each LEPG measured in (a) is below the respective reference level for each of the LEPG measured; and (d) administering the therapy when the level of mRNA expression of each LEPG measured in (a) is below the respective reference level for each of the LEPG measured, thereby treating the gastrointestinal inflammatory disorder. In one aspect, there is provided use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising: (a) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression of each of the LEPG measured in (a) to a reference level for each of the LEPG measured; and (c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured. In

some embodiments, the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2. In some embodiments, at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15. In one embodiment, 105 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one embodiment, an initial dose of 210 mg of the integrin beta7 antagonist is administered subcutaneously followed by subsequent doses, each subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously, administered at each of weeks 2, 4, 8 and 12 after the initial dose. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0026] ~~In yet still another aspect,~~Disclosed are methods of predicting the response of a patient suffering from a gastrointestinal inflammatory disorder, or predicting responsiveness of a gastrointestinal inflammatory disorder patient, to a therapy comprising an integrin beta7 antagonist ~~are provided in which expression of at least one, at least two, at least three, or at least four HEPG in a biological sample selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 are measured and in which expression of of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 are measured.~~

[0026a] In one aspect, there is provided 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:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG in a biological sample that has been obtained from the patient, selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 and comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured ("HEPG reference level"); and further comprising

(b) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 and comparing the mRNA expression level detected in the sample to a reference level for each of the LEPG measured (“LEPG reference level”); and

(c) predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured in (b) has been measured as elevated compared to the HEPG reference level and when the level of mRNA expression of each of the LEPG measured in (c) has been measured as reduced compared to the LEPG reference level.

[0026b] In one aspect, there is provided a method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising

(a) measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

and further comprising

(b) measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient;

wherein elevated mRNA expression level of each of the HEPG measured in (a) compared to a reference level for each of the HEPG measured, and wherein reduced mRNA expression level of each of the LEPG measured in (b) compared to a reference level for each of the LEPG measured, identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

[0026c] In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected

assessed by flexible sigmoidoscopy. In certain such embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0027] In another aspect, 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 which comprise: (a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured (“HEPG reference level”); and which methods further comprise (c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient; (d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured (“LEPG reference level”); and (e) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the ~~respective-HEPG reference level for each of the HEPG measured~~ and when the level of mRNA expression of each LEPG measured in (c) is below the ~~respective-LEPG reference level for each of the LEPG measured~~. In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1 and the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2. In some embodiments, at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15. In some embodiments, a further HEPG in addition to those identified above is measured, which further HEPG is ITGAE. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn’s disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal

healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0028] ~~In yet still another aspect,~~Further disclosed are methods of treating a patient having a gastrointestinal inflammatory disorder ~~are provided in which the methods comprise:~~
(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient; (b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the HEPG measured (“HEPG reference level”) and which methods further comprise (c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample from the patient; (d) comparing the level of mRNA expression of each LEPG measured in (c) to a reference level for each of the LEPG measured (“LEPG reference level”); (e) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level; and (f) administering the therapy when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level, thereby treating the gastrointestinal inflammatory disorder. In one aspect, there is provided use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as

more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising: (a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient; (b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured (“HEPG reference level”); and further comprising (c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient; (d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured (“LEPG reference level”); and (e) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level. In some embodiments, the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1 and the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2. In some embodiments, at least one, at least two, or at least three LEPG are selected

from SLC8A3, VNN2, and TNFSF15. In some embodiments, a further HEPG in addition to those identified above is measured, which further HEPG is ITGAE. In one embodiment, 105 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one embodiment, an initial dose of 210 mg of the integrin beta7 antagonist is administered subcutaneously followed by subsequent doses, each of 210 mg of the integrin beta7 antagonist administered subcutaneously, administered at each of weeks 2, 4, 8 and 12 after the initial dose. In one embodiment, the patient is a human. In one embodiment, the patient is not previously treated with an anti-TNF therapeutic agent. In one embodiment, the gastrointestinal inflammatory disorder is an inflammatory bowel disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In one embodiment, the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission. In certain embodiments, 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 embodiments, 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 embodiments, patients who experience mucosal healing are determined to have an endoscopy subscore of 0. In certain embodiments, clinical response is determined to have occurred when the patient experiences 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.

[0029] In still yet another aspect embodiment, an integrin beta7 antagonist for use in treating a patient having a gastrointestinal inflammatory disorder is provided. In certain embodiments, the patient is treated or selected for treatment when the level of mRNA expression of at least one gene selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 is above a reference level. In one embodiment, a further gene in addition to those identified above is measured, which further gene is ITGAE. In certain embodiments, the patient is treated or selected for treatment when the level of mRNA expression of at least one gene selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 is below a reference level. In one embodiment, the reference level for each gene measured is a median value. In one embodiment, the integrin beta7 antagonist is

for use in treating the patient wherein 105 mg is administered subcutaneously once every four weeks. In one embodiment, an initial dose of 210 mg of the integrin beta7 antagonist is administered subcutaneously followed by subsequent doses, each of 210 mg of the integrin beta7 antagonist administered subcutaneously, administered at each of weeks 2, 4, 8 and 12 after the initial dose.

[0030] In a further aspect ~~embodiment~~, in vitro use of at least one agent that specifically binds to a biomarker selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 is provided. In one embodiment, an agent that binds to a further biomarker in addition to those identified above is measured, which further biomarker is ITGAE. In certain 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 mRNA expression above a reference level identifies or selects that the patient is more likely to respond to the therapy. In one embodiment, the reference level is a median value. In certain embodiments, the in vitro use comprises a kit.

[0031] In yet still another aspect ~~embodiment~~, in vitro use of at least one agent that specifically binds to a biomarker selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 is provided. In certain 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 mRNA expression below a reference level identifies or selects that the patient is more likely to respond to the therapy. In one embodiment, the reference level is a median value. In certain embodiments, the in vitro use comprises a kit.

[0032] In still another aspect ~~embodiment~~, methods of treating a gastrointestinal inflammatory disorder in a patient are provided. In certain 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 some embodiments, the sample has been determined to express elevated GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, or SLC8A3 compared to the median value. In some embodiments, the sample has

been determined to express elevated mRNA levels of two or three or four of GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 compared to the median levels of the same mRNAs. In some embodiments, the sample has been determined to express elevated mRNA levels of a further gene in addition to those identified above, which further gene is ITGAE. In certain 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 embodiment, the biological sample is a tissue biopsy sample. In certain such embodiments comprising a tissue biopsy, expression of SLC8A3 has not been determined. In one embodiment, the biological sample is peripheral whole blood. In certain such embodiments comprising peripheral blood, elevated expression of SLC8A3 has been determined. In one embodiment, the peripheral whole blood is collected in a PAXgene tube. In certain embodiments, the mRNA expression level is measured by an RNA sequencing method, microarray, or PCR method. In one embodiment, the PCR method is qPCR. In certain embodiments, the measuring comprises amplifying one or more of GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 mRNA, and optionally further comprising amplifying ITGAE mRNA, and detecting the amplified mRNA, thereby measuring the level of amplified mRNA. In certain embodiments 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 embodiment, 105 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks. In one embodiment, an initial dose of 210 mg of the integrin beta7 antagonist is administered subcutaneously followed by subsequent doses, each of 210 mg of the integrin beta7 antagonist administered subcutaneously, administered at each of weeks 2, 4, 8 and 12 after the initial dose.

[0033] In still another embodiment aspect, methods of treating a gastrointestinal inflammatory disorder in a patient are provided. In certain 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 reduced mRNA expression levels of one or more of certain genes. In some embodiments, the sample has been determined to express

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, at least two, at least three, or at least four High Expression Predictive Genes ("HEPG") in the sample selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3;
 - comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured; and
 - predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured has been measured as elevated compared to the respective reference level for each of the HEPG measured.
2. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient, wherein elevated mRNA expression level of each of the HEPG measured compared to a reference level for each of the HEPG measured 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, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the respective HEPG measured; and

(c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured.

4. A method of treating a patient having a gastrointestinal inflammatory disorder, the method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the HEPG measured;

(c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured; and

(d) administering the therapy when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured, thereby treating the gastrointestinal inflammatory disorder.

5. 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, at least two, or at least three Low Expression Predictive Genes ("LEPG") in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3,

comparing the mRNA expression level of each of the LEPG measured in the sample to a reference level for each of the LEPG measured, and

predicting that the patient will respond to the therapy when the level of mRNA expression of each of the LEPG measured has been measured as reduced compared to the respective reference level for each of the LEPG measured.

6. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample from the patient, wherein reduced mRNA expression level of each of the LEPG measured compared to a reference level for each of the LEPG measured identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

7. 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, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each of the LEPG measured in (a) to a reference level for each of the LEPG measured; and

(c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured.

8. A method of treating a patient having a gastrointestinal inflammatory disorder, the method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each of the LEPG measured in (a) to a reference level for each of the LEPG measured;

(c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured; and

(d) administering the therapy when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured, thereby treating the gastrointestinal inflammatory disorder.

9. 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:

(a) obtaining a biological sample from the patient;

(b) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG in the sample selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 and comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured ("HEPG reference level"); and further comprising

(c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 and comparing the mRNA expression level detected in the sample to a reference level for each of the LEPG measured ("LEPG reference level"); and

(d) predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured in (b) has been measured as elevated compared to the HEPG reference level and when the level of mRNA expression of each of the LEPG measured in (c) has been measured as reduced compared to the LEPG reference level.

10. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising

(a) measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient;

and further comprising

(b) measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M,

MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample from the patient;

wherein elevated mRNA expression level of each of the HEPG measured in (a) compared to a reference level for each of the HEPG measured, and wherein reduced mRNA expression level of each of the LEPG measured in (b) compared to a reference level for each of the LEPG measured, identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

11. 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, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured ("HEPG reference level"); and further comprising

(c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample from the patient;

(d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured ("LEPG reference level"); and

(e) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level.

12. A method of treating a patient having a gastrointestinal inflammatory disorder, the method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1,

PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample from the patient;

(b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured ("HEPG reference level"); and further comprising

(c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample from the patient;

(d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured ("LEPG reference level"); and

(e) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level; and

(f) administering the therapy when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level, thereby treating the gastrointestinal inflammatory disorder.

13. The method of any one of claims 9-12 further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.

14. The method of any one of claims 1-4, wherein the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1.

15. The method of any one of claims 1-4 or 14 further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.

16. The method of any one of claims 5-8, wherein the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, and CCL2.

17. The method of claim 16, wherein at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15.

18. The method of any one of claims 9-12, wherein the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and

ECH1 and wherein the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2.

19. The method of claim 18, further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.

20. The method of claim 19, wherein at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15.

21. The method of any one of claims 4, 8, or 12, wherein 105 mg of the integrin beta7 antagonist is administered subcutaneously once every four weeks.

22. The method of any one of claims 4, 8, or 12, wherein an initial dose of 210 mg of the integrin beta7 antagonist is administered subcutaneously followed by a first subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously two weeks after the initial dose, a second subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously four weeks after the initial dose, a third subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously eight weeks after the initial dose, and a fourth subsequent dose of 210 mg of the integrin beta7 antagonist administered subcutaneously twelve weeks after the initial dose.

23. The method of any one of claims 1-22, wherein the gastrointestinal inflammatory disorder is an inflammatory bowel disease.

24. The method of claim 23, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.

25. The method of claim 24, wherein the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission.

26. The method of any one of claims 1-25, wherein the biological sample is selected from intestinal tissue and peripheral whole blood.

27. The method of claim 26, wherein the mRNA expression level is measured by an RNA sequencing method, microarray or a PCR method.

28. The method of claim 27, wherein the PCR method comprises qPCR.

29. The method of claim 28, wherein the measuring comprises amplifying one or more of GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, SLC8A3 mRNA, and optionally further comprising amplifying ITGAE, and detecting the amplified mRNA, thereby measuring the level of amplified mRNA.

30. The method of claim 28, wherein the measuring comprises amplifying one or more of SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP,

IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, VNN3 mRNA and detecting the amplified mRNA, thereby measuring the level of amplified mRNA.

31. The method of any one of claims 1-8, wherein each of the reference levels is a median value.
32. The method of any one of claims 9-12, wherein the HEPG reference level is a median value and the LEPG reference level is median value.
33. The method of any one of the preceding claims, wherein the patient is not previously treated with an anti-TNF therapeutic agent.
34. The method of claim 25, wherein 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) $MCS \leq 2$ with no individual subscore > 1 .
35. Use of a kit for determining the mRNA level of at least one, at least two, at least three, or at least four markers selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample obtained from a patient suffering from a gastrointestinal inflammatory disorder for stratifying patients into likely responders and non-responders for therapeutic treatment with an integrin beta7 antagonist.
36. The use according to claim 35, wherein the kit is for determining the mRNA level of at least one, at least two, at least three, or at least four markers selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1.
37. The use according to claim 35 or claim 36, wherein the kit is for further determining the mRNA level of ITGAE.
38. Use of a kit for determining the mRNA level of at least one, at least two, or at least three markers selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample obtained from a patient suffering from a gastrointestinal inflammatory disorder for stratifying patients into likely responders and non-responders for therapeutic treatment with an integrin beta7 antagonist.

39. The use according to claim 38, wherein the kit is for determining the mRNA level of at least one, at least two, or at least three markers selected from SLC8A3, TNFSF15, BEST2, and CCL2.

40. The use according to claim 38 or claim 39, wherein the kit is for further determining the mRNA level of ITGAE.

41. A kit for stratifying a patient suffering from a gastrointestinal inflammatory disorder, wherein the kit comprises:

(a) reagents for measuring the mRNA level of at least one, at least two, at least three, or at least four markers selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample obtained from the patient; and

(b) instructions for (i) measuring the mRNA level of the at least one, at least two, at least three, or at least four markers, (ii) comparing the level of the at least one, at least two, at least three, or at least four markers to a reference level, and (iii) stratifying the patient into the category of integrin beta7 antagonist responder or integrin beta7 antagonist non-responder based on the comparison.

42. The kit according to claim 41, wherein the kit comprises reagents for measuring the mRNA level of at least one, at least two, at least three, or at least four markers selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1 in the sample obtained from the patient.

43. The kit according to claim 41 or claim 42, wherein the kit further comprises reagents for measuring the mRNA level of ITGAE in the sample obtained from the patient.

44. A kit for stratifying a patient suffering from a gastrointestinal inflammatory disorder, wherein the kit comprises:

(a) reagents for measuring the mRNA level of at least one, at least two, or at least three markers selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample obtained from the patient; and

(b) instructions for (i) measuring the mRNA level of the at least one, at least two, or at least three markers, (ii) comparing the level of the at least one, at least two, or at least three markers to a reference level, and (iii) stratifying the patient into the category of integrin beta7 antagonist responder or integrin beta7 antagonist non-responder based on the comparison.

45. The kit according to claim 44, wherein the kit comprises reagents for measuring the mRNA level of at least one, at least two, or at least three markers selected from SLC8A3, TNFSF15, BEST2, and CCL2 in the sample obtained from the patient.

46. The kit according to claim 44 or claim 45, wherein the kit further comprises reagents for measuring the mRNA level of ITGAE in the sample obtained from the patient.

47. The method of any one of claims 1-34, or the use according to any one of claims 35-40, or the kit according to any one of claims 41-46, wherein the integrin beta7 antagonist is a monoclonal anti-beta7 antibody.

48. The method of claim 47, wherein the anti-beta7 antibody is selected from a chimeric antibody, a human antibody, and a humanized antibody.

49. The method of claim 48, wherein the anti-beta7 antibody is an antibody fragment.

50. The method of claim 48, 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); 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 KYASQSIG (SEQ ID NO:2), RYASQSIG (SEQ ID NO:20), or XaaYASQSIG (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.

51. The method of claim 50, 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, SEQ ID NO:16, SEQ ID NO:17 or SEQ ID NO:19.

52. The method of claim 51, wherein the anti-beta7 antibody comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:31 and a variable heavy chain comprising the amino acid sequence of SEQ ID NO:32.

53. The method of claim 52, wherein the anti-beta7 antibody is etrolizumab.

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:

measuring the level of mRNA expression of at least one, at least two, at least three, or at least four High Expression Predictive Genes ("HEPG") in a biological sample that has been obtained from the patient, selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3;

comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured; and

predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured has been measured as elevated compared to the respective reference level for each of the HEPG measured.

2. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4L1.2, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient, wherein elevated mRNA expression level of each of the HEPG measured compared to a reference level for each of the HEPG measured 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, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the respective HEPG measured; and

(c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured.

4. Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each HEPG measured in (a) to a reference level for each of the HEPG measured; and

(c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each HEPG measured in (a) is above the respective reference level for each of the HEPG measured.

5. 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, at least two, or at least three Low Expression Predictive Genes ("LEPG") in a biological sample that has been obtained from the patient, selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3,

comparing the mRNA expression level of each of the LEPG measured in the sample to a reference level for each of the LEPG measured, and

predicting that the patient will respond to the therapy when the level of mRNA expression of each of the LEPG measured has been measured as reduced compared to the respective reference level for each of the LEPG measured.

6. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from

SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient, wherein reduced mRNA expression level of each of the LEPG measured compared to a reference level for each of the LEPG measured identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

7. 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, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each of the LEPG measured in (a) to a reference level for each of the LEPG measured; and

(c) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured.

8. Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each of the LEPG measured in (a) to a reference level for each of the LEPG measured; and

(c) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the LEPG measured in (a) is below the respective reference level for each of the LEPG measured.

9. 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:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG in a biological sample that has been obtained from the patient, selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 and comparing the mRNA expression level detected in the sample to a reference level for each of the HEPG measured (“HEPG reference level”); and further comprising

(b) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG in the sample selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 and comparing the mRNA expression level detected in the sample to a reference level for each of the LEPG measured (“LEPG reference level”); and

(c) predicting that the patient will respond to the therapy when the level of mRNA expression of each of the HEPG measured in (b) has been measured as elevated compared to the HEPG reference level and when the level of mRNA expression of each of the LEPG measured in (c) has been measured as reduced compared to the LEPG reference level.

10. A method of predicting responsiveness of a gastrointestinal inflammatory disorder patient to an integrin beta7 antagonist treatment, the method comprising

(a) measuring the mRNA expression level of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

and further comprising

(b) measuring the mRNA expression level of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient;

wherein elevated mRNA expression level of each of the HEPG measured in (a) compared to a reference level for each of the HEPG measured, and wherein reduced mRNA expression level of each of the LEPG measured in (b) compared to a reference level for each of the LEPG measured, identifies the patient as one who is likely to respond to the integrin beta7 antagonist treatment.

11. 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, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured (“HEPG reference level”); and further comprising

(c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected from SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient;

(d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured (“LEPG reference level”); and

(e) identifying the patient as more likely to respond to the therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level.

12. Use of an integrin beta7 antagonist in the manufacture of a medicament for treating a patient having a gastrointestinal inflammatory disorder, wherein the patient is one who has been identified as more likely to respond to a therapy comprising the integrin beta7 antagonist by a method comprising:

(a) measuring the level of mRNA expression of at least one, at least two, at least three, or at least four HEPG selected from GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1,

PHF14, TIFAB, TMEM200A, TMIGD2, and SLC8A3 in a biological sample that has been obtained from the patient;

(b) comparing the level of mRNA expression of each of the HEPG measured in (a) to a reference level for each of the HEPG measured (“HEPG reference level”); and further comprising

(c) measuring the level of mRNA expression of at least one, at least two, or at least three LEPG selected SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1, PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, and VNN3 in the biological sample that has been obtained from the patient;

(d) comparing the level of mRNA expression of each of the LEPG measured in (c) to a reference level for each of the LEPG measured (“LEPG reference level”); and

(e) identifying the patient as more likely to respond a therapy comprising an integrin beta7 antagonist when the level of mRNA expression of each of the HEPG measured in (a) is above the HEPG reference level and the level of mRNA expression of each of the LEPG measured in (c) is below the LEPG reference level.

13. The method of any one of claims 9-11 or the use of claim 12, further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.

14. The method of any one of claims 1-3 or the use of claim 4, wherein the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1.

15. The method of any one of claims 1-3 and 14, or the use of claim 4 or 14, further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.

16. The method of any one of claims 5-7 or the use of claim 8, wherein the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, and CCL2.

17. The method or use of claim 16, wherein at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15.

18. The method of any one of claims 9-11 or the use of claim 12, wherein the at least one, at least two, at least three, or at least four HEPG are selected from GZMA, KLRB1, FOXM1, SLC8A3, and ECH1 and wherein the at least one, at least two, or at least three LEPG are selected from SLC8A3, TNFSF15, BEST2, VNN2, and CCL2.

19. The method or use of claim 18, further comprising measuring the mRNA expression level of an additional HEPG, wherein the additional HEPG is ITGAE.
20. The method or use of claim 19, wherein at least one, at least two, or at least three LEPG are selected from SLC8A3, VNN2, and TNFSF15.
21. The use of any one of claims 4, 8, or 12, wherein 105 mg of the integrin beta7 antagonist is to be administered subcutaneously once every four weeks.
22. The use of any one of claims 4, 8, or 12, wherein an initial dose of 210 mg of the integrin beta7 antagonist is to be administered subcutaneously followed by a first subsequent dose of 210 mg of the integrin beta7 antagonist to be administered subcutaneously two weeks after the initial dose, a second subsequent dose of 210 mg of the integrin beta7 antagonist to be administered subcutaneously four weeks after the initial dose, a third subsequent dose of 210 mg of the integrin beta7 antagonist to be administered subcutaneously eight weeks after the initial dose, and a fourth subsequent dose of 210 mg of the integrin beta7 antagonist to be administered subcutaneously twelve weeks after the initial dose.
23. The method or use of any one of claims 1-22, wherein the gastrointestinal inflammatory disorder is an inflammatory bowel disease.
24. The method or use of claim 23, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.
25. The method or use of claim 24, wherein the inflammatory bowel disease is ulcerative colitis and the response is selected from clinical response, mucosal healing and remission.
26. The method or use of any one of claims 1-25, wherein the biological sample is selected from intestinal tissue and peripheral whole blood.
27. The method or use of claim 26, wherein the mRNA expression level is measured by an RNA sequencing method, microarray or a PCR method.
28. The method or use of claim 27, wherein the PCR method comprises qPCR.
29. The method or use of claim 28, wherein the measuring comprises amplifying one or more of GZMA, KLRB1, FOXM1, CCDC90A, CCL4, CPA2, CXCR6, DDO, ECH1, FAM125B, FASLG, FGF9, GPR15, GZMB, KCNMA1, PHF14, TIFAB, TMEM200A, TMIGD2, SLC8A3 mRNA, and optionally further comprising amplifying ITGAE, and detecting the amplified mRNA, thereby measuring the level of amplified mRNA.
30. The method or use of claim 28, wherein the measuring comprises amplifying one or more of SLC8A3, TNFSF15, BEST2, CCL2, CCL3, CCL3L1/3, CPA3, FGF7, HAMP, IL1A, IL18RAP, INHBA, LIF, LMO4, LRRC4, MLK7.AS1, MT1M, MUCL1, MX1,

PMCH, REM2, SSTR2, TM4SF4, TMEM154, UROS, VNN2, VNN3 mRNA and detecting the amplified mRNA, thereby measuring the level of amplified mRNA.

31. The method of any one of claims 1-3 and 5-7, or the use of claim 4 or 8, wherein each of the reference levels is a median value.

32. The method of any one of claims 9-11 or the use of claim 12, wherein the HEPG reference level is a median value and the LEPG reference level is median value.

33. The method or use of any one of the preceding claims, wherein the patient is not previously treated with an anti-TNF therapeutic agent.

34. The method or use of claim 25, wherein 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 .

35. The method or use of any one of claims 1-34, wherein the integrin beta7 antagonist is a monoclonal anti-beta7 antibody.

36. The method or use of claim 35, wherein the anti-beta7 antibody is selected from a chimeric antibody, a human antibody, and a humanized antibody.

37. The method or use of claim 36, wherein the anti-beta7 antibody is an antibody fragment.

38. The method or use of claim 36, 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); 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 KYASQSIG (SEQ ID NO:2), RYASQSIG (SEQ ID NO:20), or XaaYASQSIG (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.

39. The method or use of claim 38, 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, SEQ ID NO:16, SEQ ID NO:17 or SEQ ID NO:19.

40. The method or use of claim 39, wherein the anti-beta7 antibody comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:31 and a variable heavy chain comprising the amino acid sequence of SEQ ID NO:32.

41. The method or use of claim 40, wherein the anti-beta7 antibody is etrolizumab.