CLAIMS:

1. A method of treating or preventing inflammatory bowel disease in a human subject in need thereof, the method comprising administering to the subject a composition comprising mesenchymal lineage precursor or stem cells (MLPSCs), wherein the subject is refractory to at least one biologic therapy.

2. The method of claim 1, wherein the subject is refractory to a single biologic therapy.

3. A method of treating or preventing inflammatory bowel disease in a human subject that is refractory to a single biologic therapy, the method comprising administering to the subject a composition comprising mesenchymal lineage precursor or stem cells (MLPSCs), wherein the method comprises administering a total dose of less than 600 million mesenchymal lineage precursor or stem cells.

4. The method according to any one of claims 1 to 3, wherein the biologic therapy is an anti-TNF therapy.

5. The method according to any one of claims 1 to 3, wherein the biologic therapy is infliximab, adalimumab, certolizumab pegol, vedolizumab or ustekinumab.

6. The method according to any one of claims 1 to 4, wherein the biologic therapy is infliximab or adalimumab.

7. The method according to any one of claims 1 to 6, wherein the subject is also refractory one or more of azathioprine, Mercaptopurine (6-MP), Methotrexate, cyclosporine or a steroid.

8. The method according to any one of claims 1 to 7, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

9. The method of claim 8, wherein the inflammatory bowel disease is Crohn's disease.

10. The method of claim 9, wherein the Crohn's disease presents in the rectum and/or colon of the subject.

11. The method according to any one of claims 1 to 10, wherein the subject has a C-reactive protein (CRP) level <23.

12. The method according to any one of claims 1 to 10, wherein the subject has a C-reactive protein (CRP) level <20.

13. The method according to any one of claims 1 to 12, wherein the subject has a partial clinical and/or endoscopic response at least 28 after treatment.

14. The method according to any one of claims 1 to 12, wherein the subject has a partial clinical and/or endoscopic response at least 28 to 56 days after treatment.

15. The method of claim 13 or 14 wherein partial clinical response is characterized by one or more or all of:
    - >25% reduction in C-reactive protein (CRP);
    - Decrease in CD Activity Index (CDAI) by <100 points;
    - radiographic healing as assessed via MR enterography with improvement of inflammation.

16. The method of claim 13 or 14 wherein partial endoscopic response is characterized by one or both of:
    - Decreased Simple Endoscopic Score for Crohn Disease (SES-CD) by >25% and an SES-CD < 50%;
    - SES-CD score of 10-15.

17. The method according to any one of claims 1 to 12, wherein the subject has a clinical and/or endoscopic response at least 28 after treatment.

18. The method according to any one of claims 1 to 12, wherein the subject has a clinical and/or endoscopic response at least 28 to 56 days after treatment.

19. The method of claim 17 or 18, wherein clinical response is characterized by one or more or all of:
    - Reduction in CRP by >50%;
    - Normalization of CRP;
    - ≥100 point drop in CDAI;
    - radiographic healing as assessed via MR enterography with improvement of inflammation.

20. The method of claim 17 or 18, wherein endoscopic response is characterized by one or both of:
    - Decreased SES-CD by >25% but < 50%;
    - SES-CD score of 5-10.

21. The method according to any one of claims 1 to 12, wherein the subject is in clinical and/or endoscopic remission at least 28 days after treatment.

22. The method according to any one of claims 1 to 12, wherein the subject is in clinical and/or endoscopic remission at least 28 to 56 days after treatment.

23. The method of claim 21 or 22, wherein clinical remission is characterized by one or both of:
    - normalization of CRP to <2.87 mg per litre;
    - radiographic healing as assessed via MR enterography with improvement of inflammation.

24. The method of claim 21 or 22, wherein endoscopic remission is characterized by one or both of:
    - absence of mucosal ulceration;
    - SES-CD score of 0-5.

25. The method according to any one of claims 1 to 24, wherein the composition is administered to the gastrointestinal tract wall of the subject.

26. The method according to any one of claims 1 to 25, wherein the composition is administered to the submucosal layer of the subjects gastrointestinal tract wall.

27. The method according to any one of claims 1 to 26, wherein the composition is administered to a site of inflammation in the subjects gastrointestinal tract wall.

28. The method according to any one of claims 1 to 27, wherein the composition is administered to the colon and/or rectum of the subject.

29. The method according to any one of claims 1 to 28, wherein the composition is administered via intra-luminal injection.

30. The method according to any one of claims 1 to 29, wherein the composition is administered to the submucosal layer of the subjects colon wall.

31. The method according to any one of claims 1 to 30, wherein the composition is administered to multiple sites in the subjects gastrointestinal tract wall.

32. The method according to any one of claims 1 to 24, wherein the composition is administered intravenously.

33. The method according to any one of claims 25 to 31, wherein the composition is also administered intravenously.

34. The method according to any one of claims 1 to 33, wherein the MLPSCs are mesenchymal stem cells (MSCs).

35. The method according to any one of claims 1 to 34, wherein the MLPSCs are allogeneic.

36. The method according to any one of claims 9 to 35, wherein the Crohn's disease is moderate to severe.

37. The method according to any one of claims 1 to 36, wherein the subject has a CDAI greater than 300.

38. The method according to any one of claims 9 to 37, wherein the Crohn's disease is fistulizing Crohn's disease.

39. The method according to any one of claims 1 to 31 and 33 to 38, wherein the mesenchymal lineage precursor or stem cells (MLPSCs) are administered via an endoscope.

40. The method according to any one of claims 1 to 39 which comprises administering between 1 x 10^7 and 2 x 10^8 cells.

41. The method according to any one of claims 1 to 31 and 33 to 40 which comprises administering between 1 x 10^7 and 2 x 10^8 cells to the gastrointestinal tract wall of the subject at two, three, four, five, six or more sites.

42. The method according to any one of claims 1 to 41, wherein the composition further comprises Plasma-Lyte A, dimethyl sulfoxide (DMSO), human serum albumin (HSA).

43. The method according to any one of claims 1 to 39 or 42 which comprises administering 7.5 x 10^7 cells.

44. The method according to any one of claims 1 to 39 or 42 which comprises administering 1.5 x 10^8 cells.

45. The method according to any one of claims 1 to 44, wherein the composition further comprises Plasma-Lyte A (70%), DMSO (10%), HSA (25%) solution, the HSA solution comprising 5% HSA and 15% buffer.

46. The method according to any one of claims 1 to 45, wherein the composition comprises greater than 6.68x10^6 viable cells/mL.

CLAIMS

1. Use of a composition comprising mesenchymal lineage precursor or stem cells (MLPSCs) in the manufacture of a medicament for the treatment or prevention of inflammatory bowel disease in a human subject in need thereof, in which the subject is refractory to a single biologic therapy, and in which the subject has:

a partial clinical and/or endoscopic response at least 28 days after treatment;

a clinical and/or endoscopic response at least 28 days after treatment; or

the subject is in clinical and/or endoscopic remission at least 28 days after treatment.

2. Use of a composition comprising mesenchymal lineage precursor or stem cells (MLPSCs) in the manufacture of a medicament for the treatment or prevention of inflammatory bowel disease in a human subject that is refractory to a single biologic therapy, in which a total dose of less than 600 million mesenchymal lineage precursor or stem cells are to be administered to the subject, and in which the subject has:

a partial clinical and/or endoscopic response at least 28 after treatment;

a clinical and/or endoscopic response at least 28 after treatment; or

the subject is in clinical and/or endoscopic remission at least 28 days after treatment.

3. Use according to Claim 1 or 2, in which the biologic therapy is an anti-TNF therapy.

4. Use according to Claim 1, 2 or 3, in which the biologic therapy is infliximab, adalimumab, certolizumab pegol, vedolizumab or ustekinumab.

5. Use according to any preceding claim, in which the biologic therapy is infliximab or adalimumab.

6. Use according to any preceding claim, in which the subject is also refractory one or more of azathioprine, Mercaptopurine (6-MP), Methotrexate, cyclosporine or a steroid.

7. Use according to any preceding claim, in which the inflammatory bowel disease is Crohn’s disease or ulcerative colitis.

8. Use according to Claim 7, in which the inflammatory bowel disease is Crohn’s disease.

9. Use according to Claim 8, in which the Crohn’s disease presents in the rectum and/or colon of the subject.

10. Use according to Claim 8 or 9, in which the Crohn’s disease is moderate to severe.

11. Use according to Claim 8, 9 or 10, in which the Crohn’s disease is fistulizing Crohn's disease.

12. Use according to any of Claims 8 to 11, in which the subject has a CDAI greater than 300.

13. Use according to any preceding claim, in which:

the subject has a C-reactive protein (CRP) level < 23, preferably < 20;

treatment reduces CRP by > 20% from baseline;

treatment reduces CRP to less than 2.95 mg per litre; or

treatment normalizes CRP levels in a subject.

14. Use according to any preceding claim, in which the subject has a partial clinical and/or endoscopic response at least 28 to 56 days after treatment, a clinical and/or endoscopic response at least 28 to 56 days after treatment, or is in clinical and/or endoscopic remission at least 28 to 56 days after treatment.

15. Use according to any preceding claim, in which partial clinical response is characterized by one or more or all of:

> 25% reduction in C-reactive protein (CRP);

decrease in CD Activity Index (CDAI) by < 100 points;

radiographic healing as assessed via MR enterography with improvement of inflammation; and

in which partial endoscopic response is characterized by one or both of:

decreased Simple Endoscopic Score for Crohn Disease (SES-CD) by > 25% and an SES-CD < 50%;

SES-CD score of 10-15.

16. Use according to any of Claims 1 to 14, in which clinical response is characterized by one or more or all of:

reduction in CRP by > 50%;

normalization of CRP;

≥100 point drop in CDAI;

radiographic healing as assessed via MR enterography with improvement of inflammation, and

in which endoscopic response is characterized by one or both of:

decreased SES-CD by > 25% but < 50%;

SES-CD score of 5-10.

17. Use according to any of Claims 1 to 14, in which clinical remission is characterized by one or both of:

normalization of CRP to < 2.87 mg per litre;

radiographic healing as assessed via MR enterography with improvement of inflammation, and

in which endoscopic remission is characterized by one or both of:

absence of mucosal ulceration;

SES-CD score of 0-5.

18. Use according to any preceding claim, in which the composition is:

to be administered to the gastrointestinal tract wall of the subject;

to be administered to the submucosal layer of the subject's gastrointestinal tract wall;

to be administered to a site of inflammation in the subject's gastrointestinal tract wall;

to be administered to the colon and/or rectum of the subject;

to be administered via intra-luminal injection;

to be administered to the submucosal layer of the subject's colon wall;

to be administered to multiple sites in the subject's gastrointestinal tract wall;

to be administered via an endoscope; or

to be administered intravenously.

19. Use according to any preceding claim, in which the formulation is to be administered to the submucosal layer of the subject's gastrointestinal tract wall.

20. Use according to any preceding claim, in which the formulation is to be administered to the gastrointestinal tract wall of the subject at two, three, four, five, six or more sites.

21. Use according to any preceding claim, in which the MLPSCs are mesenchymal stem cells (MSCs), and/or in which the MLPSCs are allogeneic.

22. Use according to any preceding claim, in which between 1×10^7 and 2×10^8 cells are to be administered to the subject.

23. Use according to any of Claims 1 to 21, in which 7.5×10^7 cells are to be administered to the subject.

24. Use according to any of Claims 1 to 21, in which 1.5×10^8 cells are to be administered to the subject.

25. Use according to any of Claims 1 to 21, in which the composition further comprises Plasma-Lyte A (70%), dimethyl sulfoxide (DMSO) (10%), human serum albumin (has) (25%) solution, the HSA solution comprising 5% HSA and 15% buffer, optionally in which the composition comprises greater than 6.68×10^6 viable cells/mL.