SUMMARY ~~OF THE INVENTION~~

The subject ~~invention~~ disclosure provides a pharmaceutical composition comprising: (i) at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain; and (ii) a pharmaceutically acceptable carrier; for the treatment of inflammatory bowel disease (IBD).

The subject ~~invention~~ disclosure further provides a method of treating inflammatory bowel disease comprising administering to a subject in need thereof at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain thereby treating the subject.

In one aspect, there is provided use of at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain in the manufacture of a medicament for treating inflammatory bowel disease in a subject in need thereof, wherein the medicament is to be administered to the subject.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

~~The subject invention further provides~~In one aspect, there is provided a bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

The subject ~~invention~~ disclosure also makes use of bacteriophage strain CLB_P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4675 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

For the purpose of the present ~~invention~~disclosure, a variant of a bacteriophage strain is regarded as having the same lytic activity as said bacteriophage strain if it performs at least "+" against at least one of the AIEC strains LF82, 07081, 07082, 07076 and 06075 in the "*In vitro* assay of the infectivity of bacteriophages in AIEC strains" described in Example 3 below. In a preferred embodiment, a variant is regarded as having the same lytic activity if it performs at least "+" against all five AIEC strains LF 82, LF 06075, LF 07076, LF 07081 and LF 07082 (AIEC strains LF 06075, LF 07076, LF 07081 and LF 07082 are also abbreviated herein as 06075, 07076, 07081 and 07082, respectively). These AIEC strains have been deposited by Université Lille 2 – Droit et

Santé, 42 Rue Paul Duez, 59000 Lille (France) with the French National Collection at Institut Pasteur under Accession Numbers CNCM I-4712 (LF 82), CNCM I-4713 (LF 06075), CNCM I-4714 (LF 07076), CNCM I-4715 (LF 07081) and CNCM I-4716 (LF 07082).

For the purpose of the present ~~invention~~disclosure, a variant of one of the bacteriophage strains P1 to P6, P8 and CLB_P2 is regarded as having the same phenotypic characteristics as said bacteriophage strain if it has at least 80% sequence identity on at least 70% of length, preferably at least 90% sequence identity on at least 80% of length and more preferably complete sequence identity on at least 90% of length (as determined by the BLAST algorithm) with the major capsid protein of bacteriophage wV8 (for variants of P1 to P6) or bacteriophage RB69 (for variants of P8) or bacteriophage JS98 (for variants of CLB_P2), as described below in the section "Identification of Major Capsid Proteins".

In a preferred embodiment, a variant of a bacteriophage has the same lytic activity as the bacteriophage. In another embodiment, a variant of a bacteriophage has the same lytic activity and the same phenotypic characteristics as the bacteriophage.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention provides a pharmaceutical composition comprising: (i) at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive Escherichia coli strain; and (ii) a pharmaceutically acceptable carrier; for the treatment of inflammatory bowel disease.

The subject invention further provides for a method of treating inflammatory bowel disease comprising administering to a subject in need thereof at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain thereby treating the subject.

An "*adherent-invasive Escherichia coli (AIEC) strain*" as used herein should be understood as referring to an *E. coli* strain having a mean invasion potential of equal to or higher than 0.1% in a cell culture of the intestinal cell line I-407. In other words, an AIEC strain has the ability to invade an intestinal cell culture of I-407 with an invasion

CLAIMS

1. Use of at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain in the manufacture of a medicament for treating inflammatory bowel disease in a subject in need thereof, wherein the medicament is to be administered to the subject.

2. The use according to claim 1 wherein the adherent-invasive *Escherichia coli* strain is present in one or more of the intestinal parts (small and large) of the subject.

3. The use according to claim 1 wherein the adherent-invasive *Escherichia coli* strain is LF82, a strain depicted in Table 1 herein or a strain depicted in Table 2 of *Darfeuille-Michaud et al. (2004), Gastroenterology 127:412-421.*

4. The use according to any one of claims 1 to 3 wherein the inflammatory bowel disease is Crohn's disease.

5. The use according to any one of claims 1 to 4 wherein the inflammatory bowel disease is ulcerative colitis.

6. The use according to any one of claims 1 to 5 wherein the at least one bacteriophage strain comprises the bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P1.

7. The use according to any one of claims 1 to 6 wherein the at least one bacteriophage strain comprises the bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P2.

8. The use according to any one of claims 1 to 7 wherein the at least one bacteriophage strain comprises the bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P3.

9. The use according to any one of claims 1 to 8 wherein the at least one bacteriophage strain comprises the bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P4.

10. The use according to any one of claims 1 to 9 wherein the at least one bacteriophage strain comprises the bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P5.

11. The use according to any one of claims 1 to 10 wherein the at least one bacteriophage strain comprises the bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P6.

12. The use according to any one of claims 1 to 11 wherein the at least one bacteriophage strain comprises the bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has

the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P8.

13. The use according to any one of claims 1 to 12 wherein the at least one bacteriophage strain comprises the bacteriophage strain CLB_P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4675 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain CLB_P2.

14. The use according to any one of claims 1 to 13 wherein the administration is oral administration.

15. Bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

16. Bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

17. Bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

18. Bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity,

preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

19. Bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

20. Bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

21. Bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

22. The use according to any one of claims 1 to 14 wherein the inflammatory bowel disease is recurrence of ileal lesions after surgery.

23. The use according to claim 22, wherein the surgery is to remove at least a part of the small intestine in CD patients.

CLAIMS

1. A pharmaceutical composition comprising:
   (i) at least one bacteriophage strain(s) capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain, and
   (ii) a pharmaceutically acceptable carrier;
   for use in the treatment of inflammatory bowel disease.

2. A composition according to claim 1 wherein the adherent-invasive *Escherichia coli* strain is present in one or more of the intestinal parts (small and large) of the subject.

3. A composition according to claim 1 wherein the adherent-invasive *Escherichia coli* strain is LF82, 07081, 07082, 07076 or 06075.

4. A composition according to any one of claims 1 to 3 wherein the inflammatory bowel disease is Crohn's disease.

5. A composition according to any one of claims 1 to 3 wherein the inflammatory bowel disease is ulcerative colitis.

6. A composition according to any one of claims 1 to 3 wherein the inflammatory bowel disease is recurrence of ileal lesions after surgery, for example surgery to remove at least a part of the small intestine in CD patients.

7. A composition according to any one of claims 1 to 6 wherein the composition comprises the bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P1.

8. A composition according to any one of claims 1 to 7 wherein the composition comprises the bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P2.

9. A composition according to any one of claims 1 to 8 wherein the composition comprises the bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P3.

10. A composition according to any one of claims 1 to 9 wherein the composition comprises the bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P4.

11. A composition according to any one of claims 1 to 10 wherein the composition comprises the bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P5.

12. A composition according to any one of claims 1 to 11 wherein the composition comprises the bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P6.

13. A composition according to any one of claims 1 to 12 wherein the composition comprises the bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P8.

14. A composition according to any one of claims 1 to 13 wherein the composition comprises bacteriophage strain CLB_P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4675 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain CLB_P2.

15. A method of treating inflammatory bowel disease comprising administering to a subject in need thereof at least one bacteriophage strain capable of producing a lytic infection in an adherent-invasive *Escherichia coli* strain thereby treating the subject.

16. A method according to claim 15 wherein the adherent-invasive *Escherichia coli* strain is present in one or more of the intestinal parts (small and large) of the subject.

17. A method according to claim 15 wherein the adherent-invasive *Escherichia coli* strain is LF82, a strain depicted in Table 1 herein or a strain depicted in Table 2 of *Darfeuille-Michaud et al. (2004), Gastroenterology 127:412-421.*

18. A method according to any one of claims 15 to 17 wherein the inflammatory bowel disease is Crohn's disease.

19. A method according to any one of claims 15 to 18 wherein the inflammatory bowel disease is ulcerative colitis.

20. A method according to any one of claims 15 to 19 wherein the at least one bacteriophage strain comprises the bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P1.

21. A method according to any one of claims 15 to 20 wherein the at least one bacteriophage strain comprises the bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P2.

22. A method according to any one of claims 15 to 21 wherein the at least one bacteriophage strain comprises the bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P3.

23. A method according to any one of claims 15 to 22 wherein the at least one bacteriophage strain comprises the bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P4.

24. A method according to any one of claims 15 to 23 wherein the at least one bacteriophage strain comprises the bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the

variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P5.

25. A method according to any one of claims 15 to 24 wherein the at least one bacteriophage strain comprises the bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P6.

26. A method according to any one of claims 15 to 25 wherein the at least one bacteriophage strain comprises the bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain P8.

27. A method according to any one of claims 15 to 26 wherein the at least one bacteriophage strain comprises the bacteriophage strain CLB_P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4675 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain CLB_P2.

28. A method according to any one of claims 15 to 27 wherein the administration is oral administration.

29. Bacteriophage strain P1 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4694 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

30. Bacteriophage strain P2 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4695 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

31. Bacteriophage strain P3 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4696 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

32. Bacteriophage strain P4 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4697 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

33. Bacteriophage strain P5 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4698 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

34. Bacteriophage strain P6 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4699 or a variant thereof, wherein the variant has the same lytic activity, preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.

35. Bacteriophage strain P8 deposited with the French National Collection of Microorganisms at the Institut Pasteur under Accession Number CNCM I-4700 or a variant thereof, wherein the variant has the same lytic activity,

preferably the same lytic activity and the same phenotypic characteristics as said bacteriophage strain.