ARTIFICIAL ENZYME-BACTERIA SYSTEM AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of PCT patent application No. PCT/CN2021/116214, filed 02 September 2021, the contents of it being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention generally relates to the field of biotechnology. In particular it refers to artificial enzyme systems and, more particularly, to compositions and methods for treating a gastrointestinal tract disorder using a system comprising an artificial enzyme, a probiotic bacteria and a linker.

BACKGROUND OF THE INVENTION

[0003] Gastrointestinal tract disorders include a myriad of conditions that range from a minor stomach upset or dysbiosis, to a more serious condition such as inflammatory bowel disease (IBD). Inflammatory bowel disease (IBD) describes a family of idiopathic intestinal disorders, such as Crohn's disease (CD) and ulcerative colitis (UC), that causes inflammation of the digestive tract. Such conditions can impose health and economic burdens on communities worldwide, and substantially reduce patients' quality of life.

[0004] Present clinical treatments for inflammatory bowel disease (IBD) mainly concentrate on managing the inflammatory symptoms, and generally neglect the underlying causes. Furthermore, these anti-inflammatory and immunosuppressive drugs are not completely effective, and their long-term use may lead to adverse side effects and/or serious complications.

[0005] In view of the above, there is a need to provide new and more effective treatments for inflammatory bowel disease (IBD).

SUMMARY

[0005a] In one aspect, the present disclosure refers to a system comprising:

a) an antioxidative enzyme;
b) a probiotic bacteria; and
c) a linker to conjugate the antioxidative enzyme and probiotic bacteria.

[0006] In one example, the present disclosure refers to a system comprising:

a) an artificial enzyme that facilitates a redox reaction;
b) a probiotic bacteria; and

c) a linker to conjugate the artificial enzyme and probiotic bacteria.

[0007] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the system as disclosed herein.

[0007a] In another aspect, the present disclosure refers to a use of the system as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating an inflammatory gastrointestinal tract disorder.

[0007b] In another aspect, the present disclosure refers to the system as disclosed herein or the pharmaceutical composition as disclosed herein for use in therapy.

[0008] In another example, the present disclosure refers to a method of treating a disease in a subject in need thereof by administering a therapeutically effective amount of the system or the pharmaceutical composition as disclosed herein.

[0008a] In another aspect, the present disclosure refers to a method of manufacturing the system as disclosed herein, comprising incubating (i) an antioxidative enzyme conjugated to a linker; and (ii) a probiotic bacteria, wherein the linker conjugates the antioxidative enzyme and probiotic bacteria.

[0009] In another example, the present disclosure refers to a method of manufacturing the system as disclosed herein, comprising incubating (i) an artificial enzyme conjugated to a linker; and (ii) a probiotic bacteria, wherein the linker conjugates the artificial enzyme and probiotic bacteria.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0011] **Fig. 1** shows the schematics of the artificial enzyme-probiotic bacteria system. **(a)** illustrates the general structures of the artificial enzyme-probiotic bacteria system as disclosed herein. **(b)** An exemplary artificial enzyme-probiotic bacteria system, wherein the linker has a phenylboronic acid functional group. **(c)** Another exemplary artificial enzyme-probiotic bacteria system, wherein the linker has a phenylboronic acid functional group, and a PEG. Fig. 1 provides exemplary structures of the artificial enzyme-probiotic system as disclosed herein.

[0012] **Fig. 2** is an image showing exemplary preparation of the artificial enzyme-probiotic bacteria system and their microenvironment regulations in inflammatory bowel disease (IBD)

treatment. **(a)** BL@B-SA is composed of artificial enzymes (for example, Fe SA), probiotic bacteria (for example, *Bifidobacterium longum* (BL)), and linker (for example, C18-PEG-B) to conjugate the artificial enzyme and probiotic bacteria. In this example, Fe SA is fabricated through the pyrolysis of ZIF-8 encapsulated Fe precursors (Fe@MOF). The linker C18-PEG-B comprises a hydrophobic C18 group that can be attached to Fe SA surface through noncovalent interactions and a phenylboronic acid functional group to capture bacteria *via* boronic acid vicinal-diol-based click reaction. **(b)** BL@B-SA can mimic SOD and CAT antioxidant enzymes as well as function as antioxidant molecules to scavenge multiple reactive oxygen species (ROS) to regulate the fate of cells and microbes. **(c)** Clinically used therapeutics

Claims

1. A system comprising:
    a) an antioxidative enzyme ;
    b) a probiotic bacteria; and
    c) a linker to conjugate the antioxidative enzyme and probiotic bacteria.

2. The system of claim 1, wherein the antioxidative enzyme comprises reactive oxygen species (ROS) scavenging ability to scavenge one or more reactive oxygen species (ROS).

3. The system of claim 2, wherein the antioxidative enzyme comprises reactive oxygen species (ROS) scavenging ability of reactive oxygen species (ROS) scavenging enzyme selected from a group consisting of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx).

4. The system of claim 2, wherein the antioxidative enzyme comprises reactive oxygen species (ROS) scavenging ability of an antioxidant molecule selected from a group consisting of: glutathione (GSH), cysteine (Cys), polyphenol and vitamin C.

5. The system of any one of claims 1 to 4, wherein the antioxidative enzyme comprises a nanozyme.

6. The system of claim 5, wherein the nanozyme is selected from a group consisting of a single-atom nanozyme (SAzyme), a carbon-based nanozyme and a cluster-based nanozyme.

7. The system of any one of the preceding claims, wherein the linker comprises a phenylboronic acid functional group.

8. The system of claim 7, wherein the linker further comprises polyethylene glycol (PEG).

9. The system of any one of the preceding claims, wherein the probiotic bacteria is from a genus selected from a group consisting of Bifidobacterium, Lactobacillus, Komagataeibacter and Leuconostoc.

10. The system of claim 9, wherein the probiotic bacteria is Bifidobacterium.

11. The system of claim 10, wherein the Bifidobacterium is selected from a group consisting of *Bifidobacterium longum, Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium adolescentis, Bifidobacterium infantis,* and *Bifidobacterium animalis*.

12. The system of any one of claims 1 to 11, wherein for every about 1 x 10^7 CFU probiotic bacteria, the amount of antioxidative enzyme and linker comprises 10 μg to 500 μg.

13. The system of any one of claims 1 to 12, wherein for every about 1 x 10^7 CFU probiotic bacteria, the amount of antioxidative enzyme and linker is about 50 μg.

14. A pharmaceutical composition comprising the system of any one of claims 1 to 13.

15. The pharmaceutical composition of claim 14, further comprising a pharmaceutically acceptable carrier.

16. Use of the system of any one of claims 1 to 13 or the pharmaceutical composition of claim 14 or 15 in the manufacture of a medicament for treating an inflammatory gastrointestinal tract disorder.

17. The use of claim 16, wherein the inflammatory gastrointestinal tract disorder is selected from a group consisting of inflammatory bowel disease (IBD) of ulcerative colitis, inflammatory bowel disease (IBD) of Crohn's disease, dysbiosis, necrotizing enterocolitis, acute infectious diarrhea, antibiotic-associated diarrhea, infant colic.

18. The use of any one of claims 16 to 17, comprising an effective amount of the system or the pharmaceutical composition which is to be administered, wherein the effective amount of the system or the pharmaceutical composition comprises:
- 1.0×10^7 to 3.0×10^8 CFU/kg probiotic bacteria; and
- 1.0 to 3.0 mg/kg antioxidative enzyme and linker.

19. The use of any one of claims 16 to 18, comprising an effective amount of the system or the pharmaceutical composition which is to be administered, wherein the effective amount of the system or the pharmaceutical composition comprises:
- about 2.5×10^8 CFU/kg probiotic bacteria; and
- about 1.25 mg/kg antioxidative enzyme and linker.

20. The system of any one of claims 1 to 13 or the pharmaceutical composition of claim 14 or 15 for use in therapy.

21. A method of manufacturing the system as claimed in any one of claims 1 to 13, comprising incubating (i) an antioxidative enzyme conjugated to a linker; and (ii) a probiotic bacteria, wherein the linker conjugates the antioxidative enzyme and probiotic bacteria.