

CLAIMS

1. A recombinant lactic acid bacterium (LAB) comprising a first exogenous nucleic acid encoding a fusion protein comprising (a) an N-terminal trefoil factor (TFF) polypeptide and (b) a C-terminal cell adherence polypeptide that comprises a cell-wall anchoring domain.
2. The recombinant LAB of claim 1, wherein said cell adherence polypeptide is selected from the group consisting of: a cell and mucus-binding protein A (CmbA), a mucus binding protein (Mub), a mucus adhesion promoting protein (MapA), and a lactococcal mucin binding protein (MbpL).
3. The recombinant LAB of claim 2, wherein said cell adherence polypeptide is a CmbA.
4. The recombinant LAB of claim 3, wherein said CmbA is a *Lactobacillus reuteri* CmbA.
5. The recombinant LAB of claim 2, wherein said CmbA comprises an amino acid sequence at least 80% identical to SEQ ID NO: 1.
6. The recombinant LAB of claim 1, wherein said TFF polypeptide is selected from the group consisting of: a TFF1, a TFF2, and a TFF3.
7. The recombinant LAB of claim 1, wherein said TFF polypeptide comprises an amino acid sequence at least 80% identical to SEQ ID NO: 3.
8. The recombinant LAB of claim 1, wherein said fusion protein comprises a CmbA and a human TFF3 polypeptide.
9. The recombinant LAB of claim 1, wherein said fusion protein further comprises a secretion signal peptide.

10. The recombinant LAB of claim 9, wherein said secretion signal peptide is a secretion leader of an unidentified secreted 45-kDa protein (SSusp45).
11. The recombinant LAB of claim 1, wherein said first exogenous nucleic acid is placed under the control of a promoter selected from the group consisting of: a *thyA* promoter (*PthyA*), an *hlla* promoter (*Phlla*), and a *gapB* promoter (*PgapB*).
12. The recombinant LAB of claim 1, further comprising a second exogenous nucleic acid encoding at least one therapeutic polypeptide selected from the group consisting of:
 - a) a cytokine;
 - b) an interleukin (IL);
 - c) an antibody or a functional fragment thereof;
 - d) an antigen;
 - e) a hormone;
 - f) a TFF; and
 - g) an enzyme or a functional fragment thereof.
13. The recombinant LAB of claim 12, wherein:
 - a) said interleukin (IL) is selected from the group consisting of an IL-2, an IL-10, and an IL-18;
 - b) said antibody is selected from the group consisting of an anti-TNF α antibody, an antibody to IL-4, an antibody to IL-5, an antibody to IL-13, an antibody to IL-15, and an antibody to immunoglobulin E (IgE);
 - c) said antigen is selected from the group consisting of a proinsulin (PINS), a glutamic acid decarboxylase (GAD65), an insulinoma-associated protein 2 (IA-2), an islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), a zinc transporter 8 (ZnT8), a chromogranin A, a (prepro) islet amyloid polypeptide (ppIAPP), a peripherin, a citrullinated glucose-regulated protein (GRP), a tree pollen

- allergen, a weed pollen allergen, a grass pollen allergen, a food allergen, a dust-mite allergen, a mold allergen, an animal dander allergen;
- d) said hormone selected from the group consisting of a glucagon-like peptide 1 (GLP-1), a glucagon-like peptide 2 (GLP-2), a glucagon, an exendin-4, an epidermal growth factor, and a growth hormone;
 - e) said TFF is selected from the group consisting of a TFF 1, a TFF2, and a TFF3; and
 - f) said enzyme is selected from the group consisting of a phenylalanine ammonia lyase (PAL) and an amino acid decarboxylase.
14. The recombinant LAB of claim 13, wherein said at least one therapeutic polypeptide is a PAL.
 15. The recombinant LAB of claim 12, wherein said second exogenous nucleic acid is placed under the control of a *gapB* promoter (*PgapB*).
 16. The recombinant LAB of claim 1, wherein said recombinant LAB is selected from the group consisting of a *Lactobacillus* species (sp.) bacterium, a *Bifidobacterium* sp. bacterium, a *Streptococcus* sp. bacterium, an *Enterococcus* sp. bacterium, and a *Lactococcus* sp. bacterium.
 17. The recombinant LAB of claim 16, wherein said LAB is a *Lactococcus lactis*.
 18. The recombinant LAB of claim 1, wherein said recombinant LAB has at least one feature that is different from a corresponding LAB lacking said first exogenous nucleic acid, wherein said at least one feature is selected from the group of features consisting of:
 - a) an increased gastro-intestinal (GI) transit time of at least 10%;
 - b) an increased adherence to intestinal mucosa of at least 10%;
 - c) an increased *in vitro* mucin-binding capability of at least 20%; and
 - d) an increased *in vitro* Caco-2 cell-binding capability of at least 10%.

19. The recombinant LAB of claim 18, wherein said recombinant LAB has an increased *in vitro* mucin-binding capability of at least 20% when compared with said corresponding LAB lacking said first exogenous nucleic acid.
20. The recombinant LAB of claim 18, wherein said recombinant LAB has an increased *in vitro* Caco-2 cell-binding capability of at least 10% when compared with said corresponding LAB lacking said first exogenous nucleic acid.
21. The recombinant LAB of any one of claims 1 to 20, further comprising at least one mutation or insertion that increases trehalose accumulation, wherein said at least one mutation or insertion is selected from the group consisting of:
 - a) an insertion of a first polycistronic expression cassette comprising, in 5' to 3' order, a *usp45* promoter, a *usp45* gene, an intergenic region that is immediately 5' to a *rpmD* gene, and a nucleic acid encoding an *OtsB* from *Escherichia coli*;
 - b) an insertion of a second polycistronic expression cassette comprising, in 5' to 3' order, an *hllA* promoter (*PhllA*) and a nucleic acid comprising trehalose transporter genes *llmg_0453* and *llmg_0454*;
 - c) an inactivated endogenous trehalose 6-phosphate phosphorylase gene (*trePP*), wherein said *trePP* gene is inactivated by gene deletion, so that said recombinant LAB lacks TrePP activity; and
 - d) an inactivated endogenous cellobiose-specific PTS system IIC component (*ptcC*) gene, wherein said *ptcC* gene is inactivated by insertion of a premature stop codon, so that said recombinant LAB lacks PtcC activity.
22. A pharmaceutical composition comprising said recombinant LAB of any one of claims 1-21, and a pharmaceutically acceptable carrier.

23. The recombinant LAB of any one of claims 1-21, or the pharmaceutical composition of claim 22, for use in the treatment of a disease selected from the group consisting of: an autoimmune disease, an allergy, a metabolic disease, and a gastro-intestinal disease.
24. Use of the recombinant LAB of any one of claims 1-21, or the pharmaceutical composition of claim 22, in the manufacture of a medicament for the treatment of a disease selected from the group consisting of: an autoimmune disease, an allergy, a metabolic disease, a gastro-intestinal disease, and a nutritional defect.
25. A nucleic acid encoding a fusion protein, said nucleic acid comprising:
 - a) a sequence encoding a cell-adherence polypeptide selected from the group consisting of: a cell and mucus-binding protein A (CmbA), a mucus binding protein (Mub), a mucus adhesion promoting protein (MapA), and a lactococcal mucin binding protein (MbpL); and
 - b) a sequence encoding a mucin-binding polypeptide selected from the group consisting of: a trefoil factor (TFF) polypeptide and a MucBP polypeptide.