
Claims

1. Recombinant probiotic bacteria, comprising
(a) nucleic acid sequence(s) encoding for a first heterologous factor, (a) nucleic acid sequence(s) encoding for a second heterologous factor, and preferably (a) nucleic acid sequence(s) encoding for a third heterologous factor, with the proviso that said first factor, said second factor, and said third factor are functionally different from each other,
wherein said first factor is a growth factor, wherein said second factor is selected from the group consisting of M2-polarizing factors, and wherein preferably said third factor is selected from the group consisting of M2-polarizing factors and growth factors,
wherein said M2-polarizing factor is selected from the group consisting of interleukin 4 (IL-4), interleukin 10 (IL-10), interleukin 13 (IL-13), colony stimulating factor-1 (CSF1), interleukin 34 (IL34), and mixtures thereof, and
wherein said growth factor is selected from the group consisting of fibroblast growth factors (FGF), vascular endothelial growth factors (VEGF), epidermal growth factors (EGF), heparin-binding EGF-like growth factor (HB-EGF), transforming growth factor-α (TGF-α), insulin-like growth factors (IGF), platelet-derived growth factors (PDGF), transforming growth factor beta (TGF-ß), and mixtures thereof; and
wherein the nucleic acid sequence(s) encoding for the first heterologous factor, the nucleic acid sequences(s) encoding for the second heterologous factor, and the nucleic acid sequence(s) encoding for the third heterologous factor (when present) are located in different and/or the same sub-populations of the recombinant probiotic bacteria.

2. The recombinant probiotic bacteria according to claim 1, wherein the nucleic acid sequence(s) encoding for the heterologous factors are located in one population of the recombinant probiotic bacteria.

3. Recombinant probiotic bacteria according to claim 1 or 2, wherein said nucleic acid sequence(s) is/are located on at least one of a chromosome and a plasmid of said recombinant probiotic bacteria.

4. Recombinant probiotic bacteria according to any one of claims 1-3, wherein an expression of said nucleic acid sequence(s) is/are controlled by a constitutive promoter or an inducible promoter.

5. Recombinant probiotic bacteria according to claim 4, wherein the expression of said nucleic acid sequence(s) is/are controlled by an inducible promoter, said nucleic acid sequence(s) being expressible in the presence of at least one inducer.

6. Recombinant probiotic bacteria according to any one of claims 4 or 5, wherein said inducible promoter, which is inducible by an inducer, is a promoter for a microbial gene which encodes for a lantibiotic peptide a functional analogue thereof, wherein preferably said inducible promoter is PnisA, PnisZ, PnisQ, PnisF, PnisU, or combinations thereof of *Lactococcus lactis*.

7. Recombinant probiotic bacteria according to any one of claims 5 or 6, wherein the inducer is at least one lantibiotic peptide or a functional analogue thereof, preferably selected from the group consisting of nisin A, nisin Z, nisin Q, nisin F, nisin U, functional analogues thereof, and mixtures thereof.

8. Recombinant probiotic bacteria according to any one of claims 1 to 7, wherein said probiotic bacteria further comprises at least one inactivated gene encoding for an essential protein necessary for viability of said probiotic bacteria.

9. Recombinant probiotic bacteria according to claim 8, wherein said at least one inactivated gene necessary for viability of said probiotic bacteria is selected from the group consisting of alanine racemase (alaR), thymidylate synthase (thyA), asparagine synthase (asnH), CTP synthase (pyrG), tryptophan synthase (trpBA), and combinations thereof.

10. Recombinant probiotic bacteria according to any one of claims 8 or 9, wherein said gene is inactivated by deletion of said gene, mutation of said gene, epigenetic modification of said gene, RNA interference (RNAi) mediated gene silencing of said gene, translational inhibition of said gene, or combinations thereof.

11. Recombinant probiotic bacteria according to any one of claims 1 to 10, wherein at least one of said first factor, said second factor, and said third factor is releasable from said recombinant probiotic bacteria.

12. Recombinant probiotic bacteria according to any one of claims 1 to 11, wherein said fibroblast growth factors (FGF) is selected from the group consisting of fibroblast growth factor 1, fibroblast growth factor 2, fibroblast growth factor 7 (keratinocyte growth factor), fibroblast growth factor 10 (keratinocyte growth factor 2), and mixtures thereof.

13. Recombinant probiotic bacteria according to any one of claims 1 to 12, wherein said first, second, and third heterologous factor is a combination of

- fibroblast growth factor 2, colony stimulating factor-1 and interleukin 4,
- fibroblast growth factor 2, interleukin 34 and interleukin 4,
- fibroblast growth factor 2, colony stimulating factor-1 and interleukin 13,
- fibroblast growth factor 2, interleukin 34 and interleukin 13,
- fibroblast growth factor 2, colony stimulating factor-1 and interleukin 10,
- fibroblast growth factor 2, interleukin 34 and interleukin 10,
- fibroblast growth factor 7, colony stimulating factor-1 and interleukin 4,
- fibroblast growth factor 7, interleukin 34 and interleukin 4,
- fibroblast growth factor 7, colony stimulating factor-1 and interleukin 13,
- fibroblast growth factor 7, interleukin 34 and interleukin 13,
- fibroblast growth factor 7, colony stimulating factor-1 and interleukin 10,
- fibroblast growth factor 7, interleukin 34 and interleukin 10,
- transforming growth factor beta, colony stimulating factor-1 and interleukin 4,
- transforming growth factor beta, interleukin 34 and interleukin 4,
- transforming growth factor beta, colony stimulating factor-1 and interleukin 13,
- transforming growth factor beta, interleukin 34 and interleukin 13
- transforming growth factor beta, colony stimulating factor-1 and interleukin 10,
- transforming growth factor beta, interleukin 34 and interleukin 10,
- transforming growth factor alpha, colony stimulating factor-1 and interleukin 4,
- transforming growth factor alpha, interleukin 34 and interleukin 4,
- transforming growth factor alpha, colony stimulating factor-1 and interleukin 13,
- transforming growth factor alpha, interleukin 34 and interleukin 13
- transforming growth factor alpha, colony stimulating factor-1 and interleukin 10,
- transforming growth factor alpha, interleukin 34 and interleukin 10
- platelet derived growth factor BB, colony stimulating factor-1 and interleukin 4,
- platelet derived growth factor BB, interleukin 34 and interleukin 4,
- platelet derived growth factor BB, colony stimulating factor-1 and interleukin 13,

- platelet derived growth factor BB, interleukin 34 and interleukin 13
- platelet derived growth factor BB, colony stimulating factor-1 and interleukin 10, or
- platelet derived growth factor BB, interleukin 34 and interleukin 10.

14. Recombinant probiotic bacteria according to any one of claims 1 to 13, wherein said first, second, and third heterologous factor is is a combination of fibroblast growth factor 2, colony stimulating factor-1 and interleukin 4, functional analogs thereof, and biosimilars thereof.

15. Recombinant probiotic bacteria according to any one of claims 1 to 14, wherein said recombinant probiotic bacteria are lactic acid bacteria, preferably a *Lactobacillus* or a *Lactococcus* species.

16. Recombinant probiotic bacteria according to claim 15, wherein said *Lactococcus* species is *Lactococcus lactis*, preferably *Lactococcus lactis* subspecies *cremoris*.

17. Recombinant probiotic bacteria according to any one of claims 1 to 16, wherein said recombinant probiotic bacteria are in a solution, frozen or dried, preferably lyophilised or spray dried.

18. Recombinant probiotic bacteria according to any one of claims 1 to 17, wherein said recombinant probiotic bacteria are to be administered topicallly and/or by subcutaneous injection.

19. Recombinant probiotic bacteria for use in the treatment of a chronic wound, wherein said recombinant probiotic bacteria are recombinant probiotic bacteria according to any one of claims 1 to 17.

20. Recombinant probiotic bacteria according to claim 19, wherein said chronic wound is at least one of a chronic venous ulcer, a chronic arterial ulcer, a chronic diabetic ulcer, a chronic pressure ulcer and a chronic preulceration stage thereof.