*Supplementary Material*

**Applications of genetically modified immunobiotics with high immunoregulatory capacity for treatment of inflammatory bowel diseases**

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**Supplementary Table 1. Pre-clinical evidences showing beneficial effects of gm-probiotics in treatment of GIT inflammation.**

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| --- | --- | --- | --- | --- | --- | --- |
| **Strains** | **Recombinant Protein** | **Disease model** | **Outcome** | **Efficacy** | **Potential mechanisms** | **Ref.** |
| ***Lactococcus lactis*** | | | | | | |
| MG1363 | Anti-TNF Nanobody | mDCC, m*IL-10-/-* | Reduction in HS, and IM (MPO) | CC = VC < MG1363-IL-10 = Object (mDCA)  CC = Oral/Systemic anti-TNF Nanobody = VC = MG1363-IL-10 < Object (m*IL-10-/-*) | Neutralization of TNF | (1) |
| MG1363  /NZ9000 | IL-10 | mDAC, mTAC, m*IL-10-/-* | Reduction in MS, HS, and IM (MPO, Cox-2, SAA)  Modulation of P/AICy | CC = WT/VC < Objects | Immunomodulation | (2-6) |
| MG1363 | IL-27 | mTTC, mDAC | Reduction in Mo, MS, and HS  Modulation of P/AICy, and PTc | CC = Systemic IL-27 = VC < Object  MG1363-IL-10 < Object | Immunomodulation | (7) |
| MG1363 | LcrV | mDAC, mTAC | Reduction in MS, HS, CS, and IM (MPO, PICy, Cox-2, SAA) | CC = WT < MG1363-IL-10 = Object | Immunomodulation | (3) |
| MG1363 | MAM | mDNAC | Reduction in MS, and IM (PICy) | VC < Object | Immunomodulation | (8) |
| MG1363 | TSLP | mDAC | Reduction in MS, HS, and IM (PICy)  Increase in Treg | WT < Object | Immunomodulation | (9) |
| MG1363 | TTFs | mDAC, m*IL-10-/-* | Reduction in Mo, MS, HS, and IM (MPO)  Induction of Ptgs2 expression | CC = Oral/Rectal TTF = VC = MG1363-IL-10 < Objects | Promotion of wound healing in intestinal mucosa | (10) |
| NCDO 2118 | 15-LOX-1 | mTAC | Reduction in MS, HS, LMT | CC ≤ WT ≤ Object | Reduction in oxidative stress | (11) |
| NZ3900 | Cathelicidin | mDAC | Reduction in MS, HS, CS, Ap, FMP, and IM (MPO, PICy, MDA) | CC = VC ≤ SASP ≤ Object | Promotion of wound healing in intestinal mucosa | (12, 13) |
| NZ9000 | Elafin/SLPI | mDAC, mDCC, mTTC, hIEC | Reduction in MS, HS, CT, IIP, and IM (PL, MPO, PICy, PIL) | CC ≤ WT < *L. lactis* IL-10/TGF-β < Objects | Reduction in elastolytic activity | (2, 14) |
| NZ9000 | HO-1 | mDAC | Reduction in MS, HS, and CS  Modulation of P/AICy | CC = VC < Object | Immunomodulation | (15) |
| NZ9000 | IGF-I | mDAC | Reduction in HS, CS, and IM (MPO, DAO)  Increase in occludin | CC ≤ VC ≤ Object | Improvement of intestinal barrier function | (16) |
| NZ9800 | SOD | rTAC | Reduction in MS, HS, and IM (MPO, NT) | CC < WT = Object | Reduction in oxidative stress | (17) |
| ***Lactobacillus*** | | | | | | |
| *casei* BL23 | Cat/SOD | mDAC, mTAC | Reduction in MS, HS, and LMT  Modulation of P/AICy | CC ≤ WT/VC < Objects | Reduction in oxidative stress  Immunomodulation | (18-20) |
| *casei* BLS | α-MSH | mDAC | Reduction in Mo, MS, HS, CS, and IM (MPO, NF-κB)  Modulation of P/AICy | CC ≤ WT < Object | Immunomodulation | (21) |
| *casei* CECT 5276 | IL-10 | mDAC | Reduction in MS, HS, CS, and IM (NF-κB)  Modulation of P/AICy | 5-ASA  ≤ WT + 5-ASA  < Object + 5-ASA | Immunomodulation | (22) |
| *fermentum* I5007 | Cat | mDAC | Reduction in HS, IM (NF-κB, MPO, LP)  Increase in *Lb* and *Bi* in colon | CC = VC < VE = Object | Reduction in oxidative stress | (23) |
| *fermentum* I5007 | SOD | mTAC | Reduction in MS, HS, IM (NF-κB, MPO, LP) | CC ≤ WT ≤ Object | Reduction in oxidative stress | (24) |
| *gasseri* NCK 334 | SOD | m*IL-10-/-* | Reduction in HS, IM (MPO, Cox-2)  Modulation of Ao | CC ≤ VC ≤ Object | Reduction in oxidative stress | (25) |
| *plantarum* NCIMB 8826 Int-1 | SOD | rTAC | Reduction in MS, HS, and IM (MPO, NT) | CC = WT < Object | Reduction in oxidative stress | (17) |
| **Others** | | | | | | |
| *B. longum* NCC2705 | IL-10 | mDAC | Reduction in Mo, MS, HS, CS and IM (MPO, NF-κB)  Modulation of PTc, and P/AICy | CC < WT/VC < Object | Immunomodulation | (26, 27) |
| *B. longum* HB15 | α-MSH | rDAC | Reduction in HS, and IM (MPO, NO)  Modulation of P/AIC  Increase in *Bi* in colon | CC ≤ WT < Object | Immunomodulation | (28) |
| *B. longum* HB25 | α-MSH | mDAC | Reduction in HS, and IM (MPO)  Modulation of P/AICy | CC = VC < Object | Immunomodulation | (29) |
| EcN | AvCys | mDAC, pPWD, hIEC | Reduction in MS, HS, CS, IIP, and IM (PIM, PICh, PICy)  Increase in Treg, TER | CC ≤ WT < Object | Immunomodulation  Improvement of intestinal barrier function | (30) |
| EcN | IL-10 | mDAC | Reduction in MS, CS, and IM (MDA, Fr) | CC ≤ ER2738 ≤ WT, MG1363-IL-10, Object | Immunomodulation | (31) |
| *S. thermophilus* CRL807 | Cat/SOD | mTAC | Reduction in Mo, MS, HS, and LMT  Modulation of CPIc | CC < WT < Objects | Reduction in oxidative stress  Immunomodulation | (32) |

Ref.: references, MG1363/NZ3900/NZ9000/NZ9800: *Lactococcus lactis* subsp. *cremoris* MG1363/NZ3900/NZ9000/NZ9800, NCDO 2118: *Lactococcus lactis* subsp. *lactis* NCDO 2118, *B. longum*: *Bifidobacterium longum*, EcN: *Escherichia coli* Nissle 1917, *S. thermophilus*: *Streptococcus salivarius* subsp. *thermophilus*, TNF: tumor necrosis factor, IL-10: interleukin 10, IL-27: interleukin 27, LcrV: low calcium response V antigen from *Yersinia* *pseudotuberculosis*, MAM: anti-inflammatory protein from *Faecalibacterium prausnitzii*, TSLP: thymic stromal lymphopoietin, TTFs: trefoil factors, 15-LOX-1: 15-lipoxygenase-1, SLPI: secretory leukocyte protease inhibitor, HO-1: heme oxygenase-1, IGF-I: insulin-like growth factor I, SOD: superoxide dismutase, Cat: catalase, α-MSH: α-melanocyte-stimulating hormone, AvCys: cystatin from *Acanthocheilonema viteae*, mDCC: murine dextran sulfate sodium-induced chronic colitis, m*IL-10-/-*: spontaneous colitis in IL-10 deficient mice, m/rDAC: murine/rat dextran sulfate sodium-induced acute colitis, m/rTAC: murine/rat 2,4,6-trinitrobenzene sulfonic acid-induced acute colitis, mTTC: murine T-cell transfer-induced enterocolitis, mDNAC: murine-dinitrobenzene sulfonic acid-induced acute colitis, hIEC, human intestinal epithelial cells, pPWD: porcine post-weaning diarrhea, HS: histological symptoms, IM: mediators of inflammation, MPO: myeloperoxidase activity, MS: macroscopic symptoms, Cox-2: cyclooxygenase-2 activity, SAA: serum amyloid A, P/AICy: pro-/anti-inflammatory cytokines, Mo: mortality, PTc: phenotypes of T-cell, CS: colon shortening, PICy: pro-inflammatory cytokines, Treg: regulatory T-cell, Ptgs2: prostaglandin-endoperoxide synthase 2, LMT: liver microbial translocation, Ap: apoptosis in colonic tissues, FMP: fecal microbiota populations, MDA: malonaldehyde activity, CT: colon thickening, IIP: intestinal epithelial permeability, PL: proteolytic activity, PIL: pro-inflammatory leukocytes, DAO: diamine oxidase activity, NT: nitrotyrosine, NF-κB: nuclear factor-κB, LP: lipid peroxidation, *Lb*: Lactobacilli, *Bi*: Bifidobacteria, Ao: antioxidants, NO: nitrogen monoxide, PIM: pro-inflammatory macrophages, PICh: pro-inflammatory chemokines, TER: transendothelial electrical resistance, Fr: fructosamine, CPIc: cytokine phenotypes of immune cells, CC: colitis control, VC: vector control, MG1363-IL-10: IL-10-secreting MG1363, WT: wild-type strain, SASP: sulfasalazine, NZ9000-IL-10/TGF-β: IL-10- or TGF-β-secreting NZ9000, 5-ASA: 5-aminosalicylate, VE: vitamin E, ER2738: *Escherichia coli* ER2738

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