Claims

Claim 1. A modified bacterium, wherein the bacterium comprise a hypoxia regulated essential gene expression cassette comprising an essential gene of the bacterium under the control of a strictly hypoxia inducible promoter, and the bacterium is deficient in at least one gene involved in or regulating the endogenous anti-oxidative stress response pathway or a functional expression product thereof, as compared to an unmodified starting strain, wherein the essential gene is *dapE*.

Claim 2. The modified bacterium of claim 1, wherein the strictly hypoxia inducible promoter is selected from the group consisting of pepTp, fnrSp, ysgAp, ssbp1, Hip1, BBa_I14018, BBa_R1074, Ptet-arcA, and Ptet-Fnr,

preferably the strictly hypoxia inducible promoter is ssbp1 promoter.

Claim 3. The modified bacterium of claim 1, wherein when cultured under aerobic conditions, the bacterial growth is dependent on the additional DAP or an analog thereof added to the medium.

Claim 4. The modified bacterium of claim 1, wherein the gene involved in or regulating the endogenous anti-oxidative stress response pathway is an HtrA serine protease family gene, and/or

the functional expression product of the gene involved in or regulating the endogenous anti-oxidative stress response pathway is an HtrA serine protease family related protein, and/or

the bacterium is deficient in the activity of HtrA serine protease, and/or

the gene involved in or regulating the endogenous anti-oxidative stress response pathway is *htrA*, and/or

the bacterium is deficient in *htrA*.

Claim 5. The modified bacterium of claim 1, wherein the essential gene is a gene naturally occurring in the bacterial chromosome, and the natural promoter of the essential gene is functionally replaced by the strictly hypoxia inducible promoter, whereby the expression of the essential gene in the bacterium is completely under the control of the strictly hypoxia inducible promoter.

Claim 6. The modified bacterium of claim 1, wherein the essential gene expression cassette is exogenous, and the essential gene naturally occurring in the bacterial chromosome is deleted or functionally inactivated, whereby the expression of the essential gene in the bacterium is completely under the control of the strictly hypoxia inducible promoter.

Claim 7. The modified bacterium of claim 6, wherein the exogenous essential gene expression cassette is integrated into the bacterial chromosome, or

the exogenous essential gene expression cassette is outside the bacterial chromosome, or

the exogenous essential gene expression cassette is present in a plasmid carried by the bacterium.

Claim 8. The modified bacterium of claim 1, which further comprises a pH regulated expression cassette, wherein the pH regulated expression cassette comprises a gene encoding a bacteria-derived hemolysin protein under the control of a promoter that is active under acid pH condition.

Claim 9. The modified bacterium of claim 8, wherein the bacteria-derived hemolysin protein is a gram-negative bacterial hemolysin protein.

Claim 10. The modified bacterium of claim 9, wherein the gene encoding the gram-negative bacterial hemolysin protein is *hlyA* or *hlyE*, preferably the *hlyA* or *hlyE* is derived from *Listeria monocytogenes*, *Vibrio cholerae*, or *Escherichia coli*.

Claim 11. The modified bacterium of claim 8, wherein the promoter that is active under acid pH

condition is active at pH less than 7.0, 6.9, 6.8, 6.7, 6.6, 6.5, 6.4, 6.3, 6.2, 6.1, 6.0, 5.9, 5.8, 5.7, 5.6, or 5.5,

preferably the promoter that is active under acid pH condition is selected from the group consisting of sseA, ssrA, ssaB, ssaG, ssaM, and ssaR,

more preferably the promoter that is active under acid pH condition is sseA.

Claim 12. The modified bacterium of claim 1, wherein the unmodified starting strain is a facultative anaerobic bacterium,

preferably the starting strain is *Salmonella typhimurium* SL7207.

Claim 13. The modified bacterium of claim 1, wherein the bacterium is a bacteirum of *Enterobacteriaceae*,

preferably the bacterium is a bacteirum of *Escherichia sp.*, *Salmonella* sp., *Shigella* sp., *Klebsiella* sp., *Yersinia sp.*, *Citrobacter sp.*, *Enterobacter* sp., *Serratia sp.*, *Proteus sp.*, *Morganella sp.*, *Providencia sp.*, *Hafnia sp.*, or *Pantoea sp*,

more preferably the bacterium is selected from the group consisting of *Escherichia coli*, *Enterobacter blattae* (*E.blattae*), *Enterobacter fergusonii* (*E.fergusonii*), *Enterobacter hermannii* (*E.hermannii*), *Enterobacter vulneris* (*E.vulneris*), *Salmonella enterica* (*S.enterica*), *Salmonella bongori* (*S.bongori*), *Salmonella typhi* (*S.typhi*), *Salmonella choleraesuis* (*S.choleraesuis*), *Salmonella typhimurium* (*S.typhimurium*), *Shigella dysenteriae* (*S.dysenteriae*), *Shigella flexneri* (*S.flexneri*), *Shigella boydii* (*S.boydii*), *Shigella sonnei* (*S.sonnei*), *Klebsiella pneumoniae* (*K.peumoniae*), *Klebsiella oxytoca* (*K.oxytoca*), *Yersinia pestis* (*Y.pestos*), *Yersinia enterocolitica* (*Y.enterocolitica*), *Yersinia pseudotuberculosis* (*Y.pseudotuberculosis*), *Yersinia aldouae* (*Y.aldouae*), *Yersinia bercovieri* (*Y.bercovieri*), *Yersinia frederiksenii* (*Y.frederiksenii*), *Yersinia intermedia* (*Y.intermedia*), *Yersinia kristersenii* (*Y.kristersenii*), *Yersinia mollaretti* (*Y.mollaretti*), *Yersinia rohdei* (*Y.rohdei*), *Yersinia ruckeri* (*Y.ruckeri*), *Citrobacter freundii* (*C.freundii*), *Citrobacter koseri* (*C.kaseri*), *Citrobacter braakii* (*C.braakii*), *Enterobacter aerogenes* (*E.aerogenes*), *Enterobacter cloacae* (*E.cloacae*), *Enterobacter gergoviae* (*E.gergoviac*), *Enterobacter sakazakii* (*E.sakazakii*), *Enterobacter taylorae* (*E.tavlorae*), *Enterobacter amnigenus* (*E.aminigenus*), *Enterobacter intermedius* (*E.intermedius*), *Enterobacter asburiae* (*E.asburiac*), *Enterobacter cancerogenus* (*E.cancerogenus*), *Enterobacter dissolvens* (*E.dissolvens*), *Enterobacter nimipressuralis* (*E.nimipressuralis*), *Serratia marcescens* (*S.marcescens*), *Serratia entomophila* (*S.entomophila*), *Serratia ficaria* (*S.ficaria*), *Serratia fonticola* (*S.fonticola*), *Serratia grimesii* (*S.grimesii*), *Serratia liquefaciens* (*S.liquefaciens*), *Serratia odorifera* (*S.odorifera*), *Serratia plymuthica* (*S.plymuthica*), *Serratia proteamaculans* (*S.proteamaculans*), *Serratia rubidaea* (*S. rubidaea*), *Serratia ureilytica* (*S.ureilytica*), *Proteus mirabilis* (*P.mirabilis*), *Proteus vulgaris* (*P.vulgaris*), *Proteus myxofaciens* (*P.myxofaciens*), *Proteus penneri* (*P.penneri*), *Proteus hauseri* (*P.hauseri*)), *Morganella morganii* (*M.morganii*), *Providencia alcalifaciens* (*P.alcalifaciens*), *Providencia rustigianii* (*P.rustigianii*), *Providencia stuartii* (*P.stuartii*), *Providencia rettgeri* (*P.rettgeri*), *Providencia heimbachae* (*P.heimbochae*), *Hafnia alvei* (*H.alvei*), and *Pantoea agglomerans* (*P.agglomerans*),

more preferably the bacterium is *Salmonella typhimurium*.

Claim 14. The modified bacterium of claim 1, wherein the bacterium expresses a wild-type lipopolysaccharide (LPS).

Claim 15. The modified bacterium of claim 1, wherein, when administrated to a subject with a tumor, the bacterium is capable of surviving and proliferating in tumor tissue and is rapidly cleared in normal tissue.