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(54) Compoziţii care conţin tulpini bacteriene

(57) Rezumat:

1

Invenţia furnizează compoziţii care cuprind tulpini bacteriene pentru tratarea şi prevenirea cancerului.

2

Secvenţe: 4
Revendicări: 16
Figuri: 2

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(54) Compositions comprising bacterial strains

(57) Abstract:

1

The invention provides compositions comprising bacterial strains for treating and preventing inflammatory and autoimmune diseases.

2

Sequences: 4
Claims: 16
Fig.: 2

Descriere:
(Descrierea se publică în redacţia solicitantului)

DOMENIUL TEHNIC

Această invenţie se referă la compoziţiile care conţin tulpini bacteriene izolate din tractul digestiv al mamiferelor şi utilizarea unor astfel de compoziţii în tratamentul bolii.

BAZELE INVENŢIEI

Se crede că intestinul uman este steril *in utero,* dar este expus la o mare varietate de microbi materni şi de mediu imediat după naştere. Apoi, apare o perioadă dinamică de colonizare şi succesiune microbiană, care este influenţată de factori cum ar fi modul de livrare, mediul, dieta şi genotipul gazdei, toate acestea avand impact asupra compoziţiei microbiotei intestinale, în special în timpul vieţii timpurii. Ulterior, microbiota se stabilizează şi devine similară unui adult [1]. Microbiota intestinală umană conţine mai mult de 500–1000 de filotipuri diferite aparţinând în principal două la diviziuni bacteriene majore, Bacteroidetes şi Firmicutes [2]. Relaţiile simbiotice de succes care decurg din colonizarea bacteriană a intestinului uman au oferit o mare varietate de funcţii metabolice, structurale, de protecţie şi alte beneficii. Activităţile metabolice îmbunătăţite ale intestinului colonizat asigură că alte componente dietetice nedigerabile sunt degradate, cu eliberarea de produse secundare care asigură o sursă importantă de nutrienţi pentru gazdă. În mod similar, importanţa imunologică a microbiotei intestinale este bine recunoscută şi este exemplificată în cazul animalelor fără germeni care au un sistem imunitar afectat care este reconstituit funcţional după introducerea bacteriilor comensale [3–5].

Schimbările dramatice ale compoziţiei microbiotei au fost documentate în tulburări gastro-intestinale, cum ar fi boala inflamatorie intestinală (IBD). De exemplu, nivelurile de bacterii *Clostridium* din grupul XIVa sunt reduse la pacienţii cu IBD, în timp ce numerele de *E coli* sunt crescute, ceea ce sugerează o schimbare a echilibrului simbioţilor şi patobioţilor în intestin [6–9]. Interesant, această disbioză microbiană este, de asemenea, asociată cu dezechilibre in populaţiile de celule T efectoare.

Ca o recunoaştere a efectului pozitiv potenţial pe care anumite tulpini bacteriene îl poate avea asupra intestinului animal, au fost propuse diferite tulpini pentru utilizarea in tratamentul diferitelor boli (*vezi*, de exemplu, [10–13]). De asemenea, anumite tulpini, inclusiv cele mai multe tulpini de *Lactobacillus* şi *Bifidobacterium* au fost propuse pentru a fi utilizate in tratarea diferitelor boli inflamatorii şi autoimune care nu sunt direct legate de intestine (*vezi* [14] şi [15] pentru discuţii). Cu toate acestea, relaţia dintre diferite boli şi diferite tulpini bacteriene şi efectele precise ale anumitor tulpini bacteriene asupra intestinului şi la nivel sistemic şi asupra oricăror tipuri de boli specifice sunt slab caracterizate.

Seres Health, Inc. (*vezi* [16]) speculează că bacteriile obţinute din probe de fecale pot fi utile pentru tratarea tulburărilor sistemului imunitar, dar nu sunt furnizate indicaţii cu privire la care bacterii ar fi eficiente. Seres Therapeutics, Inc. (*vezi* [70]) sugerează în continuare compoziţii bacteriene care cuprind diferite tulpini bacteriene pentru menţinerea sau restaurarea microbiotei sănătoase în tractul gastrointestinal sau pentru tratamentul unei boli gastro-intestinale.

Honda şi colab. (*vezi* [17]) descriu cum un amestec de 20 de bacterii din diferite genuri, inclusiv specii din genul Clostridium, induce proliferarea şi acumularea de celule Th17. Compoziţiile lui Honda şi colab. sunt considerate utile pentru îmbunătăţirea funcţiilor imunitare şi pentru prevenirea sau tratarea bolilor infecţioase. Totuşi, Honda şi colab. arată că pentru a trata boala autoimună şi inflamatorie la un individ, bacteriile care induc Th17 trebuie inhibate sau ucise, de exemplu, prin administrarea unui antibiotic către pacient.

Bagge şi colab. (*vezi* [71]) a explorat efectul procesării biogazului asupra speciilor bacteriene din genurile *Bacillus* şi *Clostridium*. Dahya şi colab. (*vezi* [72]) au raportat un caz de osteomielită cauzat de *Clostridium ramosum* la un pacient imunocompetent după leziuni traumatice, care nu răspunde la tratamentul antimicrobian. Farooq şi colab. (*vezi* [73]) au discutat etiologiile colitei pseudomembranoase (PMC) şi diferitele sale posibile cauze, inclusiv numeroase organisme bacteriene.

Există o cerinţă în domeniu pentru noi metode de tratare a bolilor inflamatorii şi autoimune. Există, de asemenea, o cerinţă pentru ca efectele potenţiale ale bacteriilor intestinale să fie caracterizate astfel încât să poată fi dezvoltate noi terapii care utilizează bacterii intestinale.

REZUMATUL INVENŢIEI

Autorii invenţiei au dezvoltat noi terapii pentru tratarea şi prevenirea bolilor inflamatorii şi autoimune. In particular, autorii invenţiei au dezvoltat noi terapii pentru tratarea şi prevenirea bolilor

şi stărilor mediate de către calea IL-17 sau Th17. In particular, autorii invenţiei au găsit că tulpinile bacteriene din specia *Erysipelatoclostridium ramosum* pot fi eficiente pentru tratarea şi prevenirea bolilor inflamatorii sau autoimune mediate de către calea IL-17 sau Th17. Aşa cum se descrie în exemple, administrarea orală a compoziţiilor cuprinzând *Erysipelatoclostridium ramosum* poate reduce severitatea răspunsului inflamator, inclusiv răspunsul inflamator Th17, la modelele de uveită la şoarece.

De aceea, intr-o primă aplicaţie, invenţia furnizează o compoziţie cuprinzând o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a unei boli inflamatorii sau autoimune. Autorii invenţiei au identificat faptul că tratamentul cu tulpini bacteriene din această specie poate oferi beneficii clinice în modelele de şoareci cu boli inflamatorii şi autoimune mediate de către calea IL-17 şi Th17, poate reduce nivelurile de citokine care fac parte din calea Th17, incluzand IL-17 şi poate atenua răspunsul inflamator cu Th17.

In aplicaţii particulare, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a unei boli sau stări selectate din grupul constând din: uveită; scleroză multiplă; artrită, cum ar fi artrita reumatoidă, osteoartrita, artrita psoriatică sau artrita juvenilă idiopatică; neuromielită optică (boala Devic); spondilită anchilozantă; spondiloartrită; psoriazis; lupus eritematos sistemic; boală inflamatorie intestinală, cum ar fi boala Crohn sau colita ulceroasă; boala celiaca; astm, cum ar fi astmul alergic sau astmul neutrofil; boală pulmonară obstructivă cronică (BPOC); sclerită; vasculită;

boala lui Behcet; ateroscleroza; dermatita atopica; emfizemul; parodontita; rinita alergică; şi rejetul de alografă. Efectul arătat pentru tulpinile bacteriene din genul *Erysipelatoclostridium* asupre răspunsului inflamator Th17 şi asupra bolilor mediate de către calea IL-17 şi Th17 pot oferi beneficii terapeutice pentru alte boli şi stări mediate de către calea IL-17 şi Th17, cum ar fi cele enumerate mai sus.

In aplicaţiile preferate în mod particular, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a uveitei, cum ar uveita posterioară. Autorii invenţiei au găsit că tratamentul cu tulpinile de *Erysipelatoclostridium* pot reduce incidenţa bolii şi severitatea bolii la un model de uveită la şoarece şi pot preveni sau reduce daunele retinale. În aplicaţiile preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare in tratamentul uveitei. Compoziţii folosind *Erysipelatoclostridium ramosum* poate fi deosebit de eficiente pentru tratamentul uveitei.

In alte aplicaţii preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a astmului, cum ar fi astmul neutrofil sau astmul alergic. Tratamentul cu tulpini de *Erysipelatoclostridium* poate reduce recrutarea neutrofilelor şi a eozinofilelor în plămâni, care pot ajuta la tratarea sau prevenirea astmului. In anumite aplicaţii, compoziţia este destinată utilizării într-o metodă de tratare sau prevenire a astmului neutrofilic sau a astmului eozinofilic. Compoziţiile conform invenţiei pot fi deosebit de eficiente pentru tratarea sau prevenirea astmului neutrofil şi a astmului eozinofilic. Intr-adevăr, în anumite aplicaţii, compoziţia este destinată utilizării într-o metodă de reducere a unui răspuns inflamator neutrofilic in tratamentul sau prevenirea astmului, sau compoziţia este utilizată într-o metodă de reducere a unui răspuns inflamator eozinofilic în tratamentul sau prevenirea astmului. In aplicaţiile preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum* pentru utilizare in tratamentul astmului şi, în particular, a astmului eozinofilic sau alergic. De asemenea, *Erysipelatoclostridium ramosum* poate avea un efect deosebit de pronunţat asupra neutrofilelor in modelele de astm bronşic, şi tratamentul cu *Erysipelatoclostridium ramosum* poate fi deosebit de eficient pentru tratarea astmului neutrofilic.

In alte aplicaţii preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a artritei reumatoide. Tratamentul cu tulpini de *Erysipelatoclostridium* pot oferi beneficii clinice la un model de poliartrită reumatoidă la şoarece şi pot reduce umflarea articulaţiilor. În aplicaţiile preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare in tratamentul artritei reumatoide. Compoziţiile folosind *Erysipelatoclostridium ramosum* poate fi deosebit de eficiente pentru tratarea artritei reumatoide.

In alte aplicaţii preferate, invenţia furnizează o compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a sclerozei multiple. Tratamentul cu tulpini de *Erysipelatoclostridium* poate reduce incidenţa bolii şi severitatea bolii la un model de scleroză multiplă la şoarece. În aplicaţiile preferate, invenţia

furnizează o compoziție care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare in tratamentul sclerozei multiple. Compozițiile folosind *Erysipelatoclostridium ramosum* poate fi deosebit de eficient pentru tratarea sclerozei multiple.

In anumite aplicații, compozițiile conform invenției sunt destinate utilizării într-o metodă de reducere a producției de IL-17 sau de reducere a diferențierii celulei Th17 în tratamentul sau prevenirea unei boli sau stări mediate de către calea IL-17 sau Th17. In particular, compozițiile conform invenției pot fi utilizate în reducerea producției IL-17 sau in reducerea diferențierii celulei Th17 in tratamentul sau prevenirea astmului, artritei reumatoide, sclerozei multiple sau uveitei. De preferință, invenția furnizează compoziții care cuprind o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare in reducerea producției IL-17 sau la reducerea diferențierii celulelor Th17 în tratamentul sau prevenirea astmului, artritei reumatoide, sclerozei multiple sau uveitei.

In anumite aplicații, compoziția este destinată utilizării la un pacient cu niveluri ridicate de IL-17 sau de celule Th17. Efectul prezentat de către tulpinile de *Erysipelatoclostridium* asupra uveitei, care este puternic asociat cu răspunsul inflamator Th17, înseamnă că tulpinile de *Erysipelatoclostridium* pot fi deosebit de benefice pentru astfel de pacienți.

Tulpina bacteriană din compoziția conform invenției este din specia *Erysipelatoclostridium ramosum.* De preferință, tulpina bacteriană are o secvență de rARN 16s care este cel puțin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% identică cu SEQ ID NO: 1, 2 sau 3. De preferință, identitatea este cu SEQ ID NO: 3. De preferință, tulpina bacteriană pentru utilizare conform invenției are secvența de rARN 16s reprezentată prin SEQ ID NO: 3.

In anumite aplicații, compoziția conform invenției este pentru administrare orală. Administrarea orală a tulpinilor conform invenției poate fi eficientă pentru tratarea bolilor și a condițiilor mediate de IL-17 sau Th17. De asemenea, administrarea orală este convenabilă pentru pacienți și practicieni și permite administrarea și/sau colonizarea parțială sau totală a intestinului.

In anumite aplicații, compoziția conform invenției cuprinde unul sau mai mulți excipienți sau purtători acceptabili farmaceutic.

In anumite aplicații, compoziția conform invenției cuprinde o tulpină bacteriană care a fost liofilizată. Liofilizarea este o tehnică eficientă și convenabilă pentru prepararea compozițiilor stabile care permit livrarea bacteriilor.

In anumite aplicații, invenția furnizează un produs alimentar cuprinzând compoziția descrisă mai sus.

In anumite aplicații, invenția furnizează o compoziție de vaccin cuprinzând compoziția descrisă mai sus.

In dezvoltarea invenției de mai sus, inventatorii au identificat și caracterizat o tulpină bacteriană care este deosebit de utilă pentru terapie. Tulpina de *Erysipelatoclostridium ramosum* conform invenției s-a dovedit a fi eficientă pentru tratarea bolilor descrise aici, cum ar fi uveita. De aceea, intr-un alt aspect, invenția furnizează o celulă din *Erysipelatoclostridium ramosum* tulpina MRX027 (in special MRX027 depusă ca NCIMB 42688) pentru utilizare în terapie. Invenția furnizează, de asemenea, compoziții cuprinzând astfel de celule sau culturi biologic pure de astfel de celule pentru utilizare in terapie. Invenția furnizează, de asemenea, o celulă de *Erysipelatoclostridium ramosum* tulpina MRX027 (în special MRX027 depusă ca NCIMB 42688) pentru utilizare in tratarea sau prevenirea bolilor inflamatorii sau autoimune descrise aici.

SCURTĂ DESCRIERE A DESENELOR

Figura 1: Modelul uveitei la șoarece – scorurile TEFI in grupul martor. Datele sunt prezentate ca medie ± ESM.

Figura 2: Modelul uveitei la șoarece – scorurile TEFI in ziua 28. Datele sunt prezentate ca medie ± ESM.

DESCRIEREA INVENȚIEI

Tulpini bacteriene

Compozițiile conform invenției cuprind o tulpină bacteriană din specia *Erysipelatoclostridium ramosum.* Exemplele demonstrează că bacteriile din această specie sunt utile pentru tratarea sau prevenirea uveitei și bolilor inflamatorii sau autoimune mediate de către calea IL-17 sau Th17.

Prezenta dezvăluire oferă un *Erysipelatoclostridium,* de exemplu, un *Erysipelatoclostridium ramosum* pentru utilizare in terapie, de exemplu, pentru utilizare in tratarea sau prevenirea unei boli inflamatorii și/sau autoimune. Invenția furnizează o compoziție care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum* pentru utilizare in tratarea sau prevenirea unei boli

inflamatorii şi/sau autoimune. In anumite aplicaţii, compoziţiile invenţiei cuprind *Erysipelatoclostridium ramosum,* şi nu conţin nici un alt gen bacterian. În anumite aplicaţii, compoziţiile conform invenţiei cuprind o singură specie de *Erysipelatoclostridium ramosum,* şi nu conţin alte specii bacteriene. În anumite aplicaţii, compoziţiile conform invenţiei cuprind o singură tulpină de *Erysipelatoclostridium ramosum,* şi nu conţin alte tulpini sau specii bacteriene.

Exemple de specii de *Erysipelatoclostridium* pentru utilizare în prezenta dezvăluire includ *Erysipelatoclostridium ramosum, (Clostridium) cocleatum, (C.) saccharogumia, (C.) spiroforme,* şi *(C.) innocuum* (reclasificată recent în [18]). *Erysipelatoclostridium* sunt colorate gram-pozitiv, nemotile, obligatoriu anaerobe, sub formă de tije drepte sau curbate elicoidal de 0,3–1,0 ?m × 2–4 ?m. Formarea de spori este rară sau absentă. În consecinţă, în unele aplicaţii ale invenţiei, tulpina bacteriană de *Erysipelatoclostridium ramosum* nu este sub formă sporulată, sau, dacă sunt prezenţi spori, aceştia sunt prezenţi într-cantitate minimă. Conţinutul de G + C din ADN–ul genomic este de 27–33% molar. Acestea fermentează glucoza, fructoza şi zaharoza [18]. Tipul de tulpină de *Erysipelatoclostridium ramosum* este ATCC 25582 = DSM 1402. Numărul de acces GenBank pentru secvenţa genei rARN 16S a tulpinii de *Erysipelatoclostridium ramosum* DSM 1402 este X73440 (dezvăluită aici ca SEQ ID NO: 1). Exemple de tulpini de *Erysipelatoclostridium ramosum* sunt descrise în [18]. O altă tulpină pentru utilizare în invenţie este tulpina de *Erysipelatoclostridium ramosum* JCM 1298. Numărul de acces GenBank pentru secvenţa genei rARN 16S a tulpinii de *Erysipelatoclostridium ramosum* JCM 1298 este NR_113243.1 (dezvăluită aici ca SEQ ID NO: 2).

Bacteria *Erysipelatoclostridium ramosum* testată în exemple este denumită aici tulpina MRX027. O secvenţă rARN 16S pentru tulpina MRX027 care a fost testată este furnizată în SEQ ID NO: 3. Tulpina MRX027 a fost depusă la 15 noiembrie 2016 la autoritatea internaţională de depozitare NCIMB, Ltd. (Ferguson Building, Aberdeen, AB21 9YA, Scoţia) de către 4D Pharma Research Ltd. (Life Sciences Building Building, Aberdeen, AB25 2ZS, Scoţia) număr de acces NCIMB 42688. Termenii „MRX027“ şi „MRx0027“ sunt utilizaţi aici în mod alternativ.

Tulpinile bacteriene strâns înrudite cu tulpina testată în exemple sunt, de asemenea, de aşteptat să fie eficiente pentru tratarea sau prevenirea uveitei şi a bolilor şi stărilor mediate de către calea IL-17 sau Th17. In anumite aplicaţii, tulpina bacteriană utilizată în invenţie are o secvenţă de rARN 16s care este cel puţin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% identică cu secvenţa rARN 16s a unei tulpini bacteriene de *Erysipelatoclostridium ramosum.* De preferinţă, tulpina bacteriană utilizată în invenţie are o secvenţă de rARN 16s care este cel puţin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% identică cu SEQ ID NO: 1, 2 sau 3. Preferabil, identitatea de secvenţă este cu SEQ ID NO: 3. De preferinţă, tulpina bacteriană pentru utilizare în invenţie are secvenţa rARN 16s reprezentată prin SEQ ID NO: 3.

Tulpinile bacteriene care sunt biotipuri ale tulpinilor MRX027 (in special MRX027 depuse ca NCIMB 42688), ATCC 25582 şi JCM 1298 sunt, de asemenea, de aşteptat să fie eficiente pentru tratarea sau prevenirea uveitei şi a bolilor şi stărilor mediate de către calea IL-17 sau Th17. Un biotip este o tulpină strâns înrudită care are aceleaşi caracteristici fiziologice sau biochimice, similare sau foarte asemănătoare.

Tulpinile care sunt biotipuri ale tulpinilor MRX027 (in special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298 şi care sunt adecvate pentru utilizare în invenţie pot fi identificate prin secvenţierea altor secvenţe nucleotidice pentru tulpinile MRX027 (in special a MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298. De exemplu, genomul substanţial intreg poate fi secvenţializat şi o tulpină de biotip pentru utilizare în invenţie poate avea cel puţin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9 % identitate de secvenţă în cel puţin 80% din întregul său genom (de exemplu, in cel puţin 85%, 90%, 95% sau 99% sau în întregul său genom). De exemplu, în unele aplicaţii, o tulpină de biotip are cel puţin 98% identitate de secvenţă în cel puţin 98% din genomul său sau cel puţin 99% identitate de secvenţă în 99% din genomul său. Alte secvenţe adecvate pentru utilizare in identificarea tulpinilor de biotip pot include secvenţe hsp60 sau repetitive cum ar fi BOX, ERIC, $(GTG)_5$, sau REP sau [19]. Tulpinile de biotip pot avea secvenţe cu identitate de secvenţă de cel puţin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% faţă de secvenţa corespunzătoare a tulpinilor MRX027 (in special a MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298. In unele aplicaţii, o tulpină de biotip are o secvenţă având o identitate de secvenţă de cel puţin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% faţă de secvenţa corespunzătoare a tulpinii MRX027 depusă ca NCIMB 42688 şi cuprinde o secvenţă de rARN 16S care este cel puţin 99% identică (de exemplu, cel puţin 99,5% sau cel puţin 99,9% identică) cu SEQ ID NO: 3. În unele aplicaţii, o tulpină de biotip are o secvenţă cu identitate de secvenţă de cel puţin 95%, 96%, 99% sau 99,9% faţă de secvenţa corespunzătoare a tulpinii MRX027 depusă ca NCIMB 42688 şi are rARN 16S din SEQ ID NO: 3.

In mod alternativ, tulpinile care sunt biotipuri ale tulpinilor MRX027 (in particular a MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298 şi care sunt adecvate pentru utilizare in invenţie pot fi identificate prin utilizarea tulpinilor MRX027 (în special a MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298 şi analiza fragmentului de restricţie şi/sau analiza PCR, de exemplu, prin utilizarea polimorfismului lungimii fragmentului fluorescent amplificat (FAFLP) şi a amprentei digitale a elementului ADN repetitiv (rep) – PCR sau a profilării proteinelor sau a secvenţei parţiale 16S sau 23s a rADN. În variantele preferate, astfel de tehnici pot fi utilizate pentru a identifica alte tulpini de *Erysipelatoclostridium ramosum*.

In anumite aplicaţii, tulpinile care sunt biotipuri ale tulpinilor MRX027 (în special a MRX027 depuse sub formă de NCIMB 42688), ATCC 25582 sau JCM 1298 şi care sunt adecvate pentru utilizare in invenţie sunt tulpinile care furnizează acelaşi model ca tulpinile MRX027 (în special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298 atunci când este analizată prin analiza de restricţie a ADN-ului ribozomal amplificat (ARDRA), de exemplu atunci cand se utilizează enzima de restricţie Sau3AI (pentru exemple şi metode de exemplificare *vezi*, de exemplu, [20]). In mod alternativ, tulpinile de biotip sunt identificate ca tulpini care au aceleaşi modele de fermentare a carbohidraţilor ca tulpinile MRX027 (în special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298.

Alte tulpini de *Erysipelatoclostridium ramosum* care sunt utile in compoziţiile şi metodele conform invenţiei, cum ar fi biotipurile având tulpinile MRX027 (în special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298, pot fi identificate utilizând orice metodă sau strategie adecvată, incluzând testele descrise în exemple. De exemplu, tulpinile pentru utilizare în invenţie pot fi identificate prin cultivarea în YCFA anaerobă şi/sau administrarea bacteriilor la modelul de artrită la şoarece indus de colagen de tip II şi apoi evaluarea nivelelor de citokină. În particular, tulpinile bacteriene care au tipare de creştere similare, tip metabolic şi/sau antigeni de suprafaţă pentru tulpinile MRX027 (in special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298, pot fi utile in invenţie. O tulpină utilă va avea activitate de modulare imunitară comparabilă cu tulpinile MRX027 (in special MRX027 depuse ca NCIMB 42688), ATCC 25582 sau JCM 1298. In particular, o tulpină de biotip va determina efecte asupra modelelor bolii uveită comparabile cu efectele prezentate în Exemple, care pot fi identificate prin utilizarea protocoalelor de cultură şi administrare descrise în Exemple.

O tulpină preferată în mod particular conform invenţiei este tulpina MRX027 (în special MRX027 depusă ca NCIMB 42688). Aceasta este tulpina exemplară testată în exemple şi dovedită a fi eficientă pentru tratarea bolii. Prin urmare, invenţia furnizează o celulă, cum ar fi o celulă izolată, de *Erysipelatoclostridium ramosum* tulpina MRX027 (în special MRX027 depusă ca NCIMB 42688) pentru utilizare in terapie, in special pentru bolile descrise aici. Invenţia furnizează, de asemenea, o compoziţie cuprinzând o celulă de *Erysipelatoclostridium ramosum* tulpina MRX027 (in special MRX027 depusă ca NCIMB 42688) pentru utilizare în terapie. Invenţia furnizează, de asemenea, o cultură biologică pură de *Erysipelatoclostridium ramosum* tulpina MRX027 (in special MRX027 depusă ca NCIMB 42688) pentru utilizare in terapie. Un derivat al lui *Erysipelatoclostridium ramosum* tulpina MRX027 (în special MRX027 depusă ca NCIMB 42688) poate fi o tulpină fiică (descendentă) sau o tulpină cultivată (subclonată) din original.

Un derivat al unei tulpini conform invenţiei poate fi modificat, de exemplu, la nivel genetic, fără a elimina activitatea biologică. În particular, o tulpină derivată este activă din punct de vedere terapeutic. O tulpină derivată va avea o activitate de modulare imunitară comparabilă cu *Erysipelatoclostridium ramosum* tulpina MRX027 (în special MRX027 depusă ca NCIMB 42688). În particular, o tulpină derivată va produce efecte asupra modelelor bolii uveită comparabile cu efectele prezentate in Exemple, care pot fi identificate prin utilizarea protocoalelor de cultivare şi administrare descrise în Exemple. Un derivat al tulpinii MRX027 (în special MRX027 depusă ca NCIMB 42688) va fi, în general, un biotip al tulpinii MRX027 (în special MRX027 depusă ca NCIMB 42688).

Referinţele la celulele de *Erysipelatoclostridium ramosum* tulpina MRX027 cuprind orice celule care au aceleaşi caracteristici de siguranţă şi eficacitate terapeutică ca tulpina MRX027 şi astfel de celule sunt incluse in invenţie. Referinţa la MRX027 depusă ca NCIMB 42688 se referă numai la tulpina depusă MRX027.

Secvenţa genomului *Erysipelatoclostridium ramosum* tulpina DSM 1402 este descrisă în WO 2017/089794 ca SEQ ID NO: 4. Referinţele aici la SEQ ID NO: 4 se referă la SEQ ID NO: 4 din WO 2017/089794. Această secvenţă este o schemă genomică obţinută folosind secvenţierea „puşcă" a genomului intreg şi este, de asemenea, disponibilă utilizând numărul de acces GenBank NZ_DS499659.1. In anumite aplicaţii, tulpina bacteriană pentru utilizare în invenţie are un cromozom cu identitate de secvenţă cu SEQ ID NO: 4. În unele aplicaţii, tulpina bacteriană utilizată în invenţie

are un cromozom cu identitate de secvență de cel puțin 90% (de exemplu cel puțin 92%, 94%, 95%, 96%, 97%, 98%, 99% sau 100% identitate) cu SEQ ID NO: 4 pe cel puțin 30% (de exemplu in cel puțin 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% , 95%, 96%, 97%, 98%, 99% sau 100%) din SEQ ID NO: 4. De exemplu, tulpina bacteriană utilizată în invenție poate avea un cromozom cu identitate de secvență de cel puțin 95% față de SEQ ID NO: 4 pe 35% din SEQ ID NO: 4 sau cel puțin 95% identitate de secvență cu SEQ ID NO: 4, sau cel puțin 90% identitate de secvență cu SEQ ID NO: 4 pe 70% din SEQ ID NO: 4 sau cel puțin 90% identitate de secvență cu SEQ ID NO: 4 pe 80% din SEQ ID NO: 4, sau cel puțin 90% identitate de secvență cu SEQ ID NO: 4 pe 90% din SEQ ID NO: 4 sau cel puțin 90% identitate de secvență cu SEQ ID NO: 4 pe 100% din SEQ ID NO: 4 sau o identitate de secvență de cel puțin 95% față de SEQ ID NO: 4 pe 70% din SEQ ID NO: 4 sau cel puțin 95% identitate de secvență cu SEQ ID NO: 4 pe 80% din SEQ ID NO: 4; cel puțin 95% identitate de secvență cu SEQ ID NO: 4 pe 90% din SEQ ID NO: 4 sau cel puțin 95% identitate de secvență cu SEQ ID NO: 4 pe 100% din SEQ ID NO: 4 sau cel puțin 98% identitate de secvență cu SEQ ID NO: 4 pe 70% din SEQ ID NO: 4 sau identitate de secvență de cel puțin 98% cu SEQ ID NO: 4 pe 80% din SEQ ID NO: 4 sau cel puțin 98% identitate de secvență cu SEQ ID NO: 4 pe 90% din SEQ ID NO: 4 sau identitate de secvență de cel puțin 98% pe 95% din SEQ ID NO: 4 sau identitate de secvență de cel puțin 98% cu SEQ ID NO: 4 pe 100% din SEQ ID NO: 4 sau identitate de secvență de cel puțin 99,5% cu SEQ ID NO: 4 pe 90% din SEQ ID NO: 4 sau o identitate de cel puțin 99,5% pe 95% din SEQ ID NO: 4 sau cel puțin 99,5% identitate pe 98% din SEQ ID NO: 4 sau cel puțin 99,5% identitate de secvență cu SEQ ID NO: 4 pe 100% din SEQ ID NO: 4.

In anumite aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență cu SEQ ID NO: 4 în regiunea care se învecinează cu secvența de rARN 16S. În unele aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență de cel puțin 95% (de exemplu cel puțin 96%, 97%, 98%, 99%, 99,5% sau 100%) față de secvența de 0,5 kb direct in amonte și/sau în aval de secvența rARN 16S din SEQ ID NO: 4. În unele aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență de cel puțin 95% (de exemplu cel puțin 96%, 97%, 98%, 99%, 99,5% sau 100%) față de secvența de 1kb direct în amonte și/sau în aval de secvența rARN 16S din SEQ ID NO: 4. În unele aplicații, tulpina bacteriană utilizată in invenție are un cromozom cu identitate de secvență de cel puțin 95% (de exemplu cel puțin 96%, 97%, 98%, 99%, 99,5% sau 100%) față de secvența de 1,5kb direct în amonte și/sau în aval de secvența rARNA 16S din SEQ ID NO: 4. În unele aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență de cel puțin 95% (de exemplu cel puțin 96, 97%, 98%, 99%, 99,5% sau 100%) față de secvența de 2kb direct în amonte și/sau în aval de secvența rARN 16S din SEQ ID NO: 4.

In anumite aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență cu SEQ ID NO: 4, de exemplu așa cum s-a descris mai sus, și o secvență rARN 16S cu identitate de secvență cu oricare dintre SEQ ID NO: 1, 2 sau 3, de exemplu așa cum s-a descris mai sus, de preferință cu o secvență rARN 16s care este cel puțin 99% identică cu SEQ ID NO: 3, mai preferabil care cuprinde secvența rARN 16S din SEQ ID NO: 3.

In anumite aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență cu SEQ ID NO: 4, de exemplu așa cum s-a descris mai sus, și este eficace pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune.

In anumite aplicații, tulpina bacteriană utilizată în invenție are un cromozom cu identitate de secvență cu SEQ ID NO: 4, de exemplu așa cum s-a descris mai sus și o secvență rARN 16S cu identitate de secvență cu oricare dintre SEQ ID NO: 1, 2 sau 3, de exemplu așa cum s-a descris mai sus, și este eficace pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune.

In anumite aplicații, tulpina bacteriană utilizată în invenție are o secvență de ARN 16s care este cel puțin 99%, 99,5% sau 99,9% identică cu secvența rARN 16s reprezentată prin SEQ ID NO: 3 (de exemplu, care cuprinde secvența rARN 16S din SEQ ID NO: 3) și un cromozom cu identitate de secvență de cel puțin 95% față de SEQ ID NO: 4 pe cel puțin 40% din SEQ ID NO: 4 și este eficientă pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune.

In anumite aplicații, tulpina bacteriană utilizată în invenție are o secvență de rARN 16s care este cel puțin 99%, 99,5% sau 99,9% identică cu secvența rARN 16s reprezentată prin SEQ ID NO: 3 (de exemplu, care cuprinde secvența rARN 16S din SEQ ID NO: 3) și un cromozom cu identitate de secvență de cel puțin 95% față de SEQ ID NO: 4 pe cel puțin 90% din SEQ ID NO: 4 și este eficientă pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune.

In anumite aplicații, tulpina bacteriană utilizată în invenție este o *Erysipelatoclostridium ramosum* și are o secvență rARN 16s care este cel puțin 99%, 99,5% sau 99,9% identică cu secvența ARN 16s reprezentată prin SEQ ID NO: 3 (de exemplu, care cuprinde secvența rARN 16S din SEQ

ID NO: 3) şi un cromozom cu identitate de secvenţă de cel puţin 98% (de exemplu identitate de secvenţă de cel puţin 99% sau cel puţin 99,5%) cu SEQ ID NO: 4 pe cel puţin 98% (de exemplu cel puţin 99% sau cel puţin 99,5%) din SEQ ID NO: 4 şi care este eficientă pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune.

In aplicaţiile preferate, tulpinile bacteriene din compoziţiile conform invenţiei sunt viabile şi capabile să colonizeze parţial sau total intestinul.

Utilizări terapeutice

Aşa cum s-a demonstrat in exemple, compoziţiile bacteriene conform invenţiei sunt eficiente pentru reducerea răspunsului inflamator Th17. În particular, tratamentul cu compoziţiile conform invenţiei realizează îmbunătăţiri clinice în modelele animale ale stărilor mediate de către calea IL-17 şi Th17 şi pot realiza o reducere a nivelurilor de IL-17A şi a alte citokine ale căii Th17. Prin urmare, compoziţiile conform invenţiei pot fi utile pentru tratarea sau prevenirea bolilor inflamatorii şi autoimune şi, în particular, a bolilor sau stărilor mediate de către IL-17. In particular, compoziţiile conform invenţiei pot fi utile pentru reducerea sau prevenirea creşterii răspunsului inflamator al IL-17.

Celulele Th17 sunt un subset de celule T helper care produc, de exemplu, IL-17A, IL17-F, IL-21 şi IL-22. Diferenţierea celulei Th17 şi expresia IL-17 pot fi conduse de către IL-23. Aceste citokine şi altele formează părţi importante ale căii Th17, care este o cale de semnalizare inflamatorie bine stabilită, care contribuie şi stă la baza unui număr de boli inflamatorii şi autoimune (aşa cum se descrie, de exemplu, in [21–26]). Bolile in care se activează calea Th17 sunt bolile mediate de către calea Th17. Bolile mediate de către calea Th17 pot fi ameliorate sau atenuate prin reprimarea căii Th17, care se poate face printr-o reducere a diferenţierii celulelor Th17 sau o reducere a activităţii lor sau o reducere a nivelului citokinelor căii Th17. Boli mediate de către calea Th17 pot fi caracterizate de niveluri crescute de citokine produse de celule Th17, cum ar fi IL-17A, IL-17F, IL-21, IL-22, IL-26, IL-9 (discutate in [27]). Bolile mediate de către calea Th17 pot fi caracterizate prin creşterea expresiei genelor legate de Th-17, cum ar fi Stat3 sau IL-23R. Bolile mediate de către calea Th17 pot fi asociate cu niveluri crescute de celule Th17.

IL-17 este o citokină proinflamatoare care contribuie la patogeneza mai multor boli şi condiţii inflamatorii şi autoimune. IL-17, aşa cum este utilizată aici, se poate referi la orice membru al familiei IL-17, incluzand IL-17A, IL-17B, IL-17C, IL-17D, IL-17E şi IL-17F. Stările şi condiţiile mediate de către IL-17 sunt caracterizate prin expresia ridicată a IL-17 şi/sau acumularea sau prezenţa celulelor IL-17 pozitive intr-un ţesut afectat de boală sau de condiţie. În mod similar, bolile şi condiţiile mediate de către IL-17 sunt boli şi condiţii care sunt exacerbate de niveluri ridicate de IL-17 sau o creştere a nivelurilor de IL-17 şi care sunt atenuate de nivelurile scăzute de IL-17 sau de o reducere a nivelurilor de IL-17. Răspunsul inflamator IL-17 poate fi local sau sistemic.

Exemplele de boli şi stări care pot fi mediate de IL-17 sau de calea Th17 includ uveita; scleroza multiplă; artrita, cum ar fi artrita reumatoidă, osteoartrita, artrita psoriazică sau artrita juvenilă idiopatică; neuromelita optică (boala Devic); spondilita anchilozantă; spondiloartrita; psoriazisul; lupusul eritematos sistemic; boala inflamatorie a intestinului, cum ar fi boala Crohn sau colita ulceroasă; boala celiacă; astmul, cum ar fi astmul alergic sau astmul neutrofil; boala pulmonară obstructivă cronică (BPOC); sclerita; vasculita; Boala lui Behcet; ateroscleroza; dermatita atopică; emfizemul; parodontita; rinita alergică; şi rejetul de alogrefă. În unele aplicaţii, patogeneza bolii sau condiţiei afectează intestinul. În unele aplicaţii, patogeneza bolii sau condiţiei nu afectează intestinul. In unele aplicaţii, patogeneza bolii sau condiţiei nu este localizată la nivelul intestinului. În unele aplicaţii, tratamentul sau prevenirea are loc la un alt situs decât la nivelul intestinului. În unele aplicaţii, tratamentul sau prevenirea are loc la nivelul intestinului şi, de asemenea, la un alt situs decât la nivelul intestinului. In anumite aplicaţii, boala sau condiţia este sistemică.

In anumite aplicaţii, compoziţiile conform invenţiei sunt destinate utilizării într-o metodă de reducere a producţiei de IL-17 sau de reducere a diferenţierii celulei Th17 în tratamentul sau prevenirea unei boli inflamatorii sau autoimune. In anumite aplicaţii, compoziţiile conform invenţiei sunt destinate utilizării în tratarea sau prevenirea unei boli inflamatorii sau autoimune, in care respectivul tratament sau respectiva prevenire este realizat(ă) prin reducerea sau prevenirea creşterii răspunsului inflamator Th17. În anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru tratarea unui pacient cu o boală inflamatorie sau autoimună, în care pacientul are niveluri crescute de IL-17 sau celule Th17 crescute sau prezintă un răspuns inflamator Th17. În anumite aplicaţii, pacientul poate fi diagnosticat cu o boală sau condiţie cronică inflamatorie sau autoimună sau compoziţia conform invenţiei poate fi utilizată pentru prevenirea unei boli sau condiţii inflamatorii sau autoimune care se dezvoltă într-o boală sau condiţie inflamatorie sau autoimună cronică. În anumite aplicaţii, boala sau starea poate să nu răspundă la tratamentul cu inhibitori ai TNF-α. Aceste utilizări

ale invenţiei pot fi aplicate la oricare dintre bolile sau condiţiile specifice enumerate în paragraful precedent.

Calea IL-17 şi Th17 este adesea asociată cu boli cronice inflamatorii şi autoimune, astfel incat compoziţiile conform invenţiei pot fi deosebit de utile pentru tratarea sau prevenirea bolilor cronice sau a condiţiilor enumerate mai sus. În anumite aplicaţii, compoziţiile sunt destinate utilizării la pacienţii cu boală cronică. În anumite aplicaţii, compoziţiile sunt pentru utilizare în prevenirea dezvoltării bolii cronice.

Compoziţiile conform invenţiei pot fi utile pentru tratarea bolilor şi afecţiunilor inflamatorii sau autoimune mediate de către calea IL-17 sau Th17 şi pentru tratarea răspunsului inflamator Th17, astfel incat compoziţiile conform invenţiei pot fi în mod particular utile pentru tratarea sau prevenirea bolilor cronice, tratarea sau prevenirea bolii la pacienţii care nu au răspuns la alte terapii (cum ar fi tratamentul cu inhibitori ai TNF-α) şi/sau pentru tratarea sau prevenirea leziunilor tisulare şi a simptomelor asociate cu IL-17 şi celulele Th17. De exemplu, se ştie că IL-17 activează distrugerea matricei in cartilaj şi ţesutul osos şi IL-17 are un efect inhibitor asupra producţiei de matrice în condrocite şi osteoblaste, astfel incat compoziţiile conform invenţiei pot fi utile pentru tratarea sau prevenirea eroziunii osoase sau deteriorării cartilajului.

In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei asigură o reducere sau previne o creştere a nivelurilor de IL-17, in special a nivelurilor de IL-17A. In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei asigură o reducere sau previne o creştere a nivelurilor de TNFα, IFN-γ sau IL-6. O astfel de reducere sau prevenire a nivelurilor ridicate ale acestor citokine poate fi utilă pentru tratarea sau prevenirea bolilor şi afecţiunilor inflamatorii şi autoimune, în special a celor mediate de către calea IL-17 sau Th17.

Uveită

In aplicaţiile preferate, compoziţiile conform invenţiei sunt destinate utilizării în tratarea sau prevenirea uveitei. Exemplele demonstrează că compoziţiile conform invenţiei realizează o reducere a incidenţei bolii şi a severităţii bolii intr-un model animal de uveită şi astfel pot fi utile în tratamentul sau prevenirea uveitei. Uveita este inflamaţia uveei şi poate duce la distrugerea tisulară a retinei. Aceasta poate să se prezinte în diferite forme anatomice (anterioară, intermediară, posterioară sau difuză) şi să rezulte din cauze diferite, dar înrudite, inclusiv tulburări autoimune sistemice. Calea IL-17 şi Th17 este implicată central în uveită, astfel încât eficacitatea compoziţiilor conform invenţiei pentru tratarea uveitei indică faptul că compoziţiile conform invenţiei pot fi deosebit de eficiente pentru tratarea şi prevenirea bolilor şi condiţiilor mediate de către calea IL-17 sau Th17. Referinţele [28–35] descriu niveluri serice crescute de interleukină-17A la pacienţii cu uveită, asocierea specifică a variantelor genetice de IL17A cu panveita, rolul citokinelor asociate Th17 in patogeneza uveitei autoimune experimentale, dezechilibrul dintre celulele Th17 şi celulele T în timpul uveitei autoimune monofazice experimentale, supra-reglarea IL-17A la pacienţii cu uveită şi bolile active Adamantiades-Behcet şi Vogt-Koyanagi-Harada (VKH), tratamentul uveitei neinfecţioase cu secukinumab (anticorp anti–IL-17A), şi Th17 în ochii cu uveită.

In anumite aplicaţii, uveita este uveită posterioară. Uveita posterioară prezintă în principal inflamaţia retinei şi a coroidului, iar exemplele demonstrează că compoziţiile conform invenţiei sunt eficiente pentru reducerea inflamaţiei şi a deteriorării retinei.

In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei are ca rezultat o reducere a deteriorării retinei. În anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru reducerea sau prevenirea leziunii retinei in tratamentul uveitei. In anumite aplicaţii, compoziţiile sunt destinate utilizării în tratarea pacienţilor cu uveită severă, care prezintă risc de leziuni ale retinei. În anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei are ca rezultat o reducere a inflamaţiei discului optic. În anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru reducerea sau prevenirea inflamaţiei discului optic. În anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei are ca rezultat o reducere a infiltrării ţesutului retinei cu celule inflamatorii. In anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru reducerea infiltraţiei tisulare a retinei cu celule inflamatorii. In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei are ca rezultat menţinerea sau îmbunătăţirea vederii. În anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru menţinerea sau îmbunătăţirea vederii.

In anumite aplicaţii, compoziţiile sunt destinate utilizării în tratarea sau prevenirea uveitei asociate cu o boală neinfecţioasă sau autoimună, cum ar fi boala Behçet, boala Crohn, iridocilita heterocromică Fuchs, granulomatoza cu poliangiită, uveita legată de HLA-B27, artrita idiopatică juvenilă, sarcoidoza, spondiloartrita, oftalmia simpatică, nefrita tubulointerstiţială şi sindromul de uveită sau sindromul Vogt-Koyanagi-Harada. S-a demonstrat că IL-17A este implicată, de exemplu, in bolile Behcet şi Vogt-Koyanagi-Harada.

Tratamentul sau prevenirea uveitei se poate referi, de exemplu, la ameliorarea severității simptomelor sau la prevenirea recidivei.

Cancer

In prezenta descriere, compozițiile sunt pentru utilizare în tratarea sau prevenirea cancerului. Calea IL-17 şi Th17 are un rol central în dezvoltarea şi progresul cancerului şi astfel compozițiile dezvăluite pot fi utile pentru tratarea sau prevenirea cancerului.

Deşi rolul IL-17 şi al celulelor Th17 în cancer nu sunt pe deplin înțelese, sunt cunoscute numeroase efecte pro-tumorale ale IL-17 şi celulelor Th17. De exemplu, IL-17 şi celulele Th17 pot promova angiogeneza, cresc proliferarea şi supraviețuirea celulelor tumorale şi pot activa factorii de transcriere care promovează tumorile [36–38].

Tratamentul cu compozițiile din descriere are ca rezultat o reducere a mărimii tumorii sau o reducere a creşterii tumorii. Compozițiile din descriere sunt utilizate pentru reducerea mărimii tumorii sau pentru reducerea creşterii tumorii. Compozițiile dezvăluite pot fi eficiente pentru reducerea mărimii sau a creşterii tumorii. Compozițiile dezvăluite pot fi utilizate la pacienții cu tumori solide. Compozițiile dezvăluite pot fi utilizate în reducerea sau prevenirea angiogenezei în tratamentul cancerului. IL-17 şi celulele Th17 au roluri centrale în angiogeneză. Compozițiile dezvăluite pot fi utilizate in prevenirea metastazelor.

Compozițiile dezvăluite pot fi utilizate în tratarea sau prevenirea cancerului mamar. Compozițiile dezvăluite pot fi eficiente pentru tratarea cancerului mamar, iar IL-17 şi celulele Th17 au roluri importante in cancerul mamar [39]. Compozițiile dezvăluite pot fi utilizate pentru reducerea mărimii tumorii, reducerea creşterii tumorii sau reducerea angiogenezei în tratamentul cancerului mamar. Cancerul poate fi carcinom mamar. Cancerul poate fi cancer mamar in stadiul IV.

Compozițiile dezvăluite pot fi utilizate in tratarea sau prevenirea cancerului pulmonar. Compozițiile dezvăluite pot fi eficiente pentru tratarea cancerului pulmonar, iar IL-17 şi celulele Th17 au roluri importante in cancerul pulmonar [40]. Compozițiile dezvăluite pot fi utilizate in reducerea dimensiunii tumorii, reducerea creşterii tumorii sau reducerea angiogenezei, în tratamentul cancerului pulmonar. Cancerul poate fi carcinom pulmonar.

Compozițiile dezvăluite pot fi utilizate în tratarea sau prevenirea cancerului hepatic. Compozițiile dezvăluite pot fi eficiente pentru tratarea cancerului hepatic, iar IL-17 şi celulele Th17 au roluri importante in cancerul hepatic [41]. Compozițiile dezvăluite pot fi utilizate pentru reducerea mărimii tumorii, reducerea creşterii tumorii sau reducerea angiogenezei in tratamentul cancerului hepatic. Cancerul poate fi hepatom (carcinom hepatocelular).

Compozițiile dezvăluite pot fi utilizate în tratarea sau prevenirea carcinomului. Compozițiile dezvăluite pot fi deosebit de eficiente pentru tratarea carcinomului. Compozițiile dezvăluite pot fi utilizate in tratarea sau prevenirea cancerului non-imunogen. Compozițiile dezvăluite pot fi eficiente pentru tratarea cancerelor non–imunogene.

Compozițiile dezvăluite pot fi utilizate pentru tratarea sau prevenirea leucemiei limfoblastice acute (ALL), a leucemiei mieloide acute, a carcinomului adrenocortical, a carcinomului bazocelular, a cancerului de duct biliar, a cancerului de vezică urinară, a tumorii osoase, a osteosarcomului/histiocitomului fibros malign, gliomului trunchiului cerebral, tumorii cerebrale, astrocitomului cerebelar, astrocitomului cerebral/ gliomului malign, ependimomului, meduloblastomului, tumorilor neuroectodermice primitive supratentoriale, cancerului mamar, adenomului/carcinoamelor bronhiale, limfomului Burkitt, tumorii carcinoide, cancerului cervical, leucemiei limfocitare cronice, leucemiei mielogene cronice, tulburărilor mieloproliferative cronice, cancerului de colon, limfomului cutanat cu celule T, cancerului endometrial, ependimomului, cancerului esofagian, sarcomului Ewing, melanomului intraocular, retinoblastomului, cancerului vezicii biliare, cancerului gastric, tumorii carcinoide gastrointestinale, tumorii stromale gastrointestinale (GIST), tumorii celulei germinale, gliomului, căii vizuale şi hipotalamice a copilăriei, limfomului Hodgkin, melanomului, carcinomului celulelor insule, sindromului Kaposi, cancerului celulei renale, cancerului laringian, leucemiei, limfomului, mezoteliomului, neuroblastomului, limfomului non-Hodgkin, cancerului orofaringian, osteosarcomului, cancerului ovarian, cancerului pancreatic, cancerului paratiroidian, cancerului faringian, adenomului hipofizar, cancerului de prostată, carcinomului celulelor renale, retinoblastomului, sarcomului, cancerului testicular, cancerului tiroidian sau cancerului uterin.

Compozițiile dezvăluite pot fi deosebit de eficiente atunci când sunt utilizate în combinație cu alți agenți terapeutici. Efectele imunomodulatoare ale compozițiilor dezvăluite pot fi eficiente atunci cand sunt combinate cu agenți anticanceroşi mai direcți. Prin urmare, compoziția dezvăluită poate cuprinde o tulpină bacteriană din genul *Erysipelatoclostridium* şi un agent anticanceros. Agentul anticanceros poate fi un inhibitor imunitar, un agent imunoterapeutic anticorp direcționat, o terapie cu

celule CAR-T, un virus oncolitic sau un medicament citostatic. Compoziția dezvăluită poate cuprinde un agent anticanceros selectat din grupul constand din: Yervoy (ipilimumab, BMS); Keytruda (pembrolizumab, Merck); Opdivo (nivolumab, BMS); MEDI4736 (AZ/MedImmune); MPDL3280A (Roche/Genentech); Tremelimumab (AZ/ MedImmune); CT-011 (pidilizumab, CureTech); BMS-986015 (lirilumab, BMS); MEDI0680 (AZ/MedImmune); MSB-0010718C (Merck); PF-05082566 (Pfizer); MEDI6469 (AZ/MedImmune); BMS-986016 (BMS); BMS-663513 (urelumab, BMS); IMP321 (Prima Biomed); LAG525 (Novartis); ARGX-110 (arGEN-X); PF-5082466 (Pfizer); CDX-1127 (varlilumab; CellDex Therapeutics); TRX-518 (GITR Inc.); MK-4166 (Merck); JTX-2011 (Jounce Therapeutics); ARGX-115 (arGEN-X); NLG-9189 (indoximod, NewLink Genetics); INCB024360 (Incyte); IPH2201 (Innate Immoterapeutics/AZ); NLG-919 (NewLink Genetics); anti-VISTA (JnJ); Epacadostat (INCB24360, Incyte); F001287 (Flexus/BMS); CP 870893 (Universitatea din Pennsylvania); MGA271 (Macrogenix); Emactuzumab (Roche/Genentech); Galunisertib (Eli Lilly); Ulocuplumab (BMS); BKT140/BL8040 (Biokine Therapeutics); Bavituximab (Peregrine Pharmaceuticals); CC 90002 (Celgene); 852A (Pfizer); VTX-2337 (VentiRx Pharmaceuticals); IMO-2055 (Hybridon, Idera Pharmaceuticals); LY2157299 (Eli Lilly); EW-7197 (Universitatea pentru femei Ewha, Coreea); Vemurafenib (Plexxikon); Dabrafenib (Genentech/GSK); BMS-777607 (BMS); BLZ945 (Memorial Sloan-Kettering Cancer Center); Unituxin (dinutuximab, United Therapeutics Corporation); Blincito (blinatumomab, Amgen); Cyramza (ramucirumab, Eli Lilly); Gazyva (obinutuzumab, Roche/Biogen); Kadcilla (ado-trastuzumab emtansină, Roche/Genentech); Perjeta (pertuzumab, Roche/Genentech); Adcetris (brentuximab vedotin, Takeda/Millennium); Arzerra (ofatumumab, GSK); Vectibix (panitumumab, Amgen); Avastin (bevacizumab, Roche/Genentech); Erbitux (cetuximab, BMS/Merck); Bexxar (tositumomab-I131, GSK); Zevalin (ibritumomab tiuxetan, Biogen); Campath (alemtuzumab, Bayer); Mylotarg (gemtuzumab ozogamicin, Pfizer); Herceptin (trastuzumab, Roche/Genentech); Rituxan (rituximab, Genentech/Biogen); volociximab (Abbvie); Enavatuzumab (Abbvie); ABT-414 (Abbvie); Elotuzumab (Abbvie/BMS); ALX-0141 (Ablynx); Ozaralizumab (Ablynx); Actimab-C (Actinium); Actimab-P (Actinium); Milatuzumab-dox (Actinium); Emab-SN-38 (Actinium); Naptumonmab estafenatox (Active Biotech); AFM13 (Affimed); AFM11 (Affimed); AGS-16C3F (Agensys); AGS-16M8F (Agensys); AGS-22ME (Agensys); AGS-15ME (Agensys); GS-67E (Agensys); ALXN6000 (samalizumab, Alexion); ALT-836 (Altor Bioscience); ALT-801 (Altor Bioscience); ALT-803 (Altor Bioscience); AMG780 (Amgen); AMG 228 (Amgen); AMG820 (Amgen); AMG172 (Amgen); AMG595 (Amgen); AMG110 (Amgen); AMG232 (adecatumumab, Amgen); AMG211 (Amgen/MedImmune); BAY20-10112 (Amgen/ Bayer); Rilotumumab (Amgen); Denosumab (Amgen); AMP-514 (Amgen); MEDI575 (AZ/MedImmune); MEDI3617 (AZ/MedImmune); MEDI6383 (AZ/MedImmune); MEDI551 (AZ/MedImmune); Moxetumomab pasudotox (AZ/MedImmune); MEDI565 (AZ/ MedImmune); MEDI0639 (AZ/MedImmune); MEDI0680 (AZ/MedImmune); MEDI562 (AZ/MedImmune); AV-380 (AVEO); AV203 (AVEO); AV299 (AVEO); BAY79-4620 (Bayer); Anetumab ravtansină (Bayer); vantictumab (Bayer); BAY94-9343 (Bayer); Sibrotuzumab (Boehringer Ingleheim); BI-836845 (Boehringer Ingleheim); B-701 (BioClin); BIIB015 (Biogen); Obinutuzumab (Biogen/Genentech); BI-505 (Bioinvent); BI-1206 (Bioinvent); TB-403 (Bioinvent); BT-062 (Biotest), BIL-010t (Biosceptor); MDX-1203 (BMS); MDX-1204 (BMS); Necitumumab (BMS); CAN-4 (Cantargia AB); CDX-011 (Celldex); CDX1401 (Celldex); CDX301 (Celldex); U3-1565 (Daiichi Sankyo); patritumab (Daiichi Sankyo); tigatuzumab (Daiichi Sankyo); nimotuzumab (Daiichi Sankyo); DS-8895 (Daiichi Sankyo); DS-8873 (Daiichi Sankyo); DS-5573 (Daiichi Sankyo); MORab-004 (Eisai); MORab-009 (Eisai); MORab-003 (Eisai); MORab-066 (Eisai); LY3012207 (Eli Lilly); LY2875358 (Eli Lilly); LY2812176 (Eli Lilly); LY3012217 (Eli Lilly); LY2495655 (Eli Lilly); LY3012212 (Eli Lilly); LY3012211 (Eli Lilly); LY3009806 (Eli Lilly); cixutumumab (Eli Lilly); Flanvotumab (Eli Lilly); IMC-TR1 (Eli Lilly); Ramucirumab (Eli Lilly); Tabalumab (Eli Lilly); Zanolimumab (Emergent Biosolution); FG-3019 (FibroGen); FPA008 (Five Prime Therapeutics); FP-1039 (Five Prime Therapeutics); FPA144 (Five Prime Therapeutics); catumaxomab (Fresenius Biotech); IMAB362 (Ganymed); IMAB027 (Ganymed); HuMax-CD74 (Genmab); HuMax-TFADC (Genmab); GS-5745 (Gilead); GS-6624 (Gilead); OMP-21M18 (demcizumab, GSK); mapatumumab (GSK); IMGN289 (ImmunoGen); IMGN901 (ImmunoGen); IMGN853 (ImmunoGen); IMGN529 (ImmunoGen); IMMU-130 (Immunomedics); milatuzumab-dox (Immunomedics); IMMU-115 (Immunomedics); IMMU-132 (Immunomedics); IMMU-106 (Immunomedics); IMMU-102 (Immunomedics); Epratuzumab (Immunomedics); Clivatuzumab (Immunomedics); IPH41 (Innate Immunotherapeutics); Daratumumab (Janssen/Genmab); CNTO-95 (Intetumumab, Janssen); CNTO-328 (siltuximab, Janssen); KB004 (KaloBios); mogamulizumab (Kyowa Hakko Kirrin); KW-2871 (ecromeximab, Life Science); Sonepcizumab (Lpath); Margetuximab (Macrogenics); Enoblituzumab (Macrogenics);

MGD006 (Macrogenics); MGF007 (Macrogenics); MK-0646 (dalotuzumab, Merck); MK-3475 (Merck); Sym004 (Symphogen/Merck Serono); DI17E6 (Merck Serono); MOR208 (Morphosys); MOR202 (Morphosys); Xmab5574 (Morphosys); BPC-1C (ensituximab, Precision Biologics); TAS266 (Novartis); LFA102 (Novartis); BHQ880 (Novartis/Morphosys); QGE031 (Novartis); HCD122 (lucatumumab, Novartis); LJM716 (Novartis); AT355 (Novartis); OMP-21M18 (Demizzumab, OncoMed); OMP52M51 (Oncomed/GSK); OMP-59R5 (Oncomed/GSK); vantictumab (Oncomed/Bayer); CMC-544 (inotuzumab ozogamicin, Pfizer); PF-03446962 (Pfizer); PF-04856884(Pfizer); PSMA-ADC (Progenics); REGN1400 (Regeneron); REGN910 (nesvacumab, Regeneron/Sanofi); REGN421 (enoticumab, Regeneron/Sanofi); RG7221, RG7356, RG7155, RG7444, RG7116, RG7458, RG7598, RG7599, RG7600, RG7636, RG7450, RG7593, RG7596, DCDS3410A, RG7414 (parsatuzumab); RG7160 (imgatuzumab); RG7159 (obintuzumab); RG7686, RG3638 (onartuzumab), RG7597 (Roche/Genentech); SAR307746 (Sanofi); SAR566658 (Sanofi); SAR650984 (Sanofi); SAR153192 (Sanofi); SAR3419 (Sanofi); SAR256212 (Sanofi), SGN-LIV1A (lintuzumab, Seattle Genetics); SGN-CD33A (Seattle Genetics); SGN-75 (vorsetuzumab mafodotin, Seattle Genetics); SGN-19A (Seattle Genetics) SGN-CD70A (Seattle Genetics); SEA-CD40 (Seattle Genetics); ibritumomab tiuxetan (Spectrum); MLN0264 (Takeda); ganitumab (Takeda/Amgen); CEP-37250 (Teva); TB-403 (Thrombogenic); VB4-845 (Viventia); Xmab2512 (Xencor); Xmab5574 (Xencor); nimotuzumab (YM Biosciences); Carlumab (Janssen); NY-ESO TCR (Adaptimmune); MAGE-A-10 TCR (Adaptimmune); CTL019 (Novartis); JCAR015 (Juno Therapeutics); KTE-C19 CAR (Kite Pharma); UCART19 (Cellectis); BPX-401 (Bellicum Pharmaceuticals); BPX-601 (Bellicum Pharmaceuticals); ATTCK20 (Unum Therapeutics); CAR-NKG2D (Celyad); Onyx-015 (Onyx Pharmaceuticals); H101 (Shanghai Sunwaybio); DNX-2401 (ADNtrix); VCN-01 (VCN Biosciences); Colo-Adl (PsiOxus Therapeutics); ProstAtak (Advantagene); Oncos-102 (Oncos Therapeutics); CG0070 (Cold Genesys); Pexa-vac (JX-594, Jennerex Biotherapeutics); GL-ONC1 (Genelux); T-VEC (Amgen); G207 (Medigene); HF10 (Takara Bio); SEPREHVIR (HSV1716, Virttu Biologics); OnenX010 (OrienGene Biotechnology); Reolizin (Oncolytics Biotech); SW-001 (Neotropix); Cacatak (CVA21, Viralytics); Alimta (Eli Lilly), cisplatină, oxaliplatină, irinotecan, acid folinic, metotrexat, ciclofosfamidă, 5–fluorouracil, Zykadia (Novartis), Tafinlar (GSK), Xalkori (Pfizer), Iressa (AZ), Gilotrif (Boehringer Ingelheim), Tarceva (Astellas Pharma), Halaven (Eisai Pharma), Veliparib (Abbvie), AZD9291 (AZ), Alectinib (Chugai), LDK378 (Novartis), Genetespib (Synta Pharma), Tergenpumatucel-L (NewLink Genetics), GV1001 (Kael-GemVax), Tivantinib (ArQule); Cytoxan (BMS); Oncovin (Eli Lilly); Adriamicyn (Pfizer); Gemzar (Eli Lilly); Xeloda (Roche); Ixempra (BMS); Abraxan (Celgene); Trelstar (Debiopharm); Taxotere (Sanofi); Nexavar (Bayer); IMMU-132 (Immunomedics); E7449 (Eisai); Thermodox (Celsion); Cometriq (Exellxis); Lonsurf (Taiho Pharmaceuticals); Camptosar (Pfizer); UFT (Taiho Pharmaceuticals); şi TS-1 (Taiho Pharmaceuticals).

In unele aplicaţii, una sau mai multe tulpini bacteriene de *Erysipelatoclostridium ramosum* este/sunt singurii agenţi terapeutic activi într-o compoziţie conform invenţiei. În unele aplicaţii, tulpina sau bacteriile bacteriene din compoziţie sunt singurii agenţi terapeutic activi într-o compoziţie conform invenţiei.

Astm

In aplicaţiile preferate, compoziţiile conform invenţiei sunt utilizate pentru tratarea sau prevenirea astmului. Compoziţiile conform invenţiei pot realiza o reducere a recrutării neutrofilelor şi/sau a eozinofilelor în căile respiratorii după sensibilizare şi provocare cu extract de praf domestic şi astfel pot fi utile în tratamentul sau prevenirea astmului. Astmul este o boală cronică caracterizată prin inflamaţia şi restricţia căilor respiratorii. Inflamaţia în astm poate fi mediată de IL-17 şi/sau celule Th17 şi astfel compoziţiile conform invenţiei pot fi deosebit de eficiente pentru prevenirea sau tratarea astmului. Inflamaţia în astm poate fi mediată de eozinofile şi/sau de neutrofile.

In anumite aplicaţii, astmul este astm eozinofilic sau alergic. Astmul eozinofilic şi alergic se caracterizează prin creşterea numărului de eozinofile în sângele periferic şi în secreţiile căilor respiratorii şi este asociat patologic cu îngroşarea zonei membranelor de bază şi farmacologic cu răspunsul la corticosteroizi [42]. Compoziţiile care reduc sau inhibă recrutarea sau activarea eozinofilelor pot fi utile pentru tratarea sau prevenirea astmului eozinofilic şi alergic.

In aplicaţii suplimentare, compoziţiile conform invenţiei sunt destinate utilizării în tratarea sau prevenirea astmului neutrofilic (sau a astmului non-eozinofilic). Numerele mari de neutrofile sunt asociate cu astm sever, care poate fi insensibil la tratamentul cu corticosteroizi. Compoziţiile care reduc sau inhibă recrutarea sau activarea neutrofilelor pot fi utile pentru tratarea sau prevenirea astmului neutrofil.

Astmul eozinofilic şi neutrofilic nu sunt condiţii care se exclud reciproc, iar tratamentele care ajută la abordarea răspunsurilor fie eozinofilic fie neutrofilic pot fi utile pentru tratarea astmului in general. Nivelurile crescute ale IL-17 şi activarea căii Th17 sunt asociate cu astm sever, astfel încât compoziţiile conform invenţiei pot fi utile pentru prevenirea dezvoltării astmului sever sau pentru tratarea astmului sever.

In anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate în metodele de reducere a răspunsului inflamator eozinofilic în tratamentul sau prevenirea astmului sau pentru utilizarea in metodele de reducere a răspunsului inflamator neutrofilic în tratamentul sau prevenirea astmului. Aşa cum s-a menţionat mai sus, nivelurile ridicate de eozinofile în astm sunt asociate patologic cu ingroşarea zonei membranelor bazale, astfel încât reducerea răspunsului inflamator eozinofilic în tratamentul sau prevenirea astmului poate fi capabilă să abordeze în mod specific această caracteristică a bolii. De asemenea, neutrofilele crescute, fie în combinaţie cu eozinofilele crescute, fie in absenţa lor, sunt asociate cu astm bronşic sever şi îngustarea cronică a căilor respiratorii. Prin urmare, reducerea răspunsului inflamator neutrofilic poate fi utilă în special pentru tratarea astmului sever.

In anumite aplicaţii, compoziţiile reduc infiltraţia peribronchiolară în astmul alergic sau sunt utilizate pentru reducerea infiltrării peribronchiolare în tratamentul astmului alergic. În anumite aplicaţii, compoziţiile reduc infiltrarea peribronchiolară şi/sau perivasculară în astmul neutrofilic sau sunt utilizate pentru reducerea infiltraţiei peribronchiolare şi/sau perivasculare în tratamentul astmului neutrofilic alergic.

In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei asigură o reducere sau previn o creştere a nivelelor de TNFα.

In anumite aplicaţii, compoziţiile conform invenţiei sunt destinate utilizării într-o metodă de tratare a astmului care are ca rezultat o reducere a răspunsului inflamator eozinofilic şi/sau neutrofilic. In anumite aplicaţii, pacientul care urmează să fie tratat are, sau a fost identificat anterior ca având nivele crescute de neutrofile sau eozinofile, de exemplu identificate prin analiza sangelui sau a sputei.

Compoziţiile conform invenţiei pot fi utile pentru prevenirea dezvoltării astmului la un nou-născut atunci când sunt administrate nou-născutului sau unei femei însărcinate. Compoziţiile pot fi utile pentru prevenirea dezvoltării astmului la copii. Compoziţiile conform invenţiei pot fi utile pentru tratarea sau prevenirea astmului la debut la adulţi. Compoziţiile conform invenţiei pot fi utile pentru gestionarea sau ameliorarea astmului. Compoziţiile conform invenţiei pot fi în mod particular utile pentru reducerea simptomelor asociate cu astmul care este agravat de alergeni, cum ar fi acarienii din praful domestic.

Tratamentul sau prevenirea astmului se poate referi, de exemplu, la o atenuare a severităţii simptomelor sau la o reducere a frecvenţei exacerbărilor sau a gamei de declanşatoare care reprezintă o problemă pentru pacient.

Artrită

In aplicaţiile preferate, compoziţiile conform invenţiei sunt utilizate pentru tratarea sau prevenirea artritei reumatoide (RA). Compoziţiile conform invenţiei pot realiza o reducere a semnelor clinice ale RA intr-un model de şoarece, pot reduce leziunea cartilajului şi a osului şi pot reduce răspunsul inflamator IL-17 şi astfel pot fi utile în tratamentul sau prevenirea RA. RA este o afecţiune sistemică inflamatorie care afectează în primul rând articulaţiile. RA este asociată cu un răspuns inflamator care are ca rezultat umflarea articulaţiilor, hiperplazia sinovială şi distrugerea cartilajului şi a osului. IL-17 şi celulele Th17 pot avea un rol cheie în RA, de exemplu deoarece IL-17 inhibă producţia de matrice in condrocite şi osteoblaste şi activează producţia şi funcţia metaloproteinazelor matrice şi deoarece activitatea bolii RA este corelată cu nivelurile de IL-17 şi numerele de celule Th17 [43,44], astfel incat compoziţiile conform invenţiei pot fi deosebit de eficiente pentru prevenirea sau tratarea RA.

In anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru scăderea nivelurilor de IL-17 sau pentru prevenirea creşterii nivelurilor de IL-17 in tratamentul sau prevenirea RA. In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei asigură o reducere sau previne o creştere a nivelurilor de IL-17, in special a nivelurilor de IL-17A. In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei asigură o reducere sau previne o creştere a nivelelor IFN-γ sau IL-6.

In anumite aplicaţii, tratamentul cu compoziţiile conform invenţiei are ca rezultat o reducere a umflării articulaţiilor. În anumite aplicaţii, compoziţiile conform invenţiei sunt destinate utilizării la pacienţii cu articulaţii umflate sau la pacienţii identificaţi ca având riscul de a avea articulaţii umflate. In anumite aplicaţii, compoziţiile conform invenţiei sunt utilizate pentru o metodă de reducere a umflării articulaţiilor in RA.

In anumite aplicații, tratamentul cu compozițiile conform invenției are ca rezultat o reducere a deteriorării cartilajului sau a deteriorării osoase. În anumite aplicații, compozițiile conform invenției sunt destinate utilizării în reducerea sau prevenirea deteriorării cartilajului sau oaselor in tratamentul RA. In anumite aplicații, compozițiile sunt destinate utilizării în tratarea pacienților cu RA severă care prezintă riscul de afectare a cartilajului sau oaselor.

Nivelurile IL-17 şi numărul celulelor Th17 crescute sunt asociate cu distrugerea cartilajului şi a osului în RA [43,44]. IL-17 este cunoscută pentru că activează distrugerea matricei în cartilaj şi țesutul osos şi IL-17 are un efect inhibitor asupra producției de matrice în condrocite şi osteoblaste. De aceea, in anumite aplicații, compozițiile conform invenției sunt utilizate pentru prevenirea eroziunii osoase sau a deteriorării cartilajelor în tratamentul RA. În anumite aplicații, compozițiile sunt destinate utilizării în tratarea pacienților care prezintă eroziune osoasă sau deteriorare a cartilajului sau pacienți identificați ca fiind expuși riscului de eroziune osoasă sau deteriorare a cartilajului.

TNF-α este de asemenea asociat cu RA, dar TNF-α nu este implicat in patogeneza etapelor ulterioare ale bolii. In contrast, IL-17 are un rol in toate stadiile bolii cronice [45]. De aceea, in anumite aplicații, compozițiile conform invenției sunt destinate utilizării în tratarea RA cronică sau RA in stadiu tardiv, cum ar fi boala care include distrugerea articulațiilor şi pierderea cartilajului. În anumite aplicații, compozițiile conform invenției sunt pentru tratarea pacienților care au primit anterior terapie anti-TNF-α. In anumite aplicații, pacienții care urmează a fi tratați nu răspund sau nu mai răspund la terapia anti-TNF-α.

Compozițiile conform invenției pot fi utile pentru modularea sistemului imunitar al pacientului, astfel incat, in anumite aplicații, compozițiile invenției sunt utilizate pentru prevenirea RA la un pacient care a fost identificat ca avand risc de RA sau care a fost diagnosticat cu RA in stadiu timpuriu. Compozițiile conform invenției pot fi utile pentru prevenirea dezvoltării RA.

Compozițiile conform invenției pot fi utile pentru gestionarea sau ameliorarea RA. Compozițiile conform invenției pot fi deosebit de utile pentru reducerea simptomelor asociate cu umflarea articulațiilor sau cu distrugerea oaselor. Tratamentul sau prevenirea RA se poate referi, de exemplu, la ameliorarea severității simptomelor sau la reducerea frecvenței exacerbărilor sau a gamei de declanşatoare care reprezintă o problemă pentru pacient.

Scleroză multiplă

In aplicațiile preferate, compozițiile conform invenției sunt pentru utilizare în tratarea sau prevenirea sclerozei multiple. Compozițiile conform invenției pot realiza o reducere a incidenței bolii şi a severității bolii într-un model de scleroză multiplă la şoarece (modelul EAE) şi astfel pot fi utile în tratamentul sau prevenirea sclerozei multiple. Scleroza multiplă este o afecțiune inflamatorie asociată cu deteriorarea tecii de mielină a neuronilor, în special în creier şi coloana vertebrală. Scleroza multiplă este o boală cronică, care este incapacitantă progresiv şi care evoluează în episoade. IL-17 şi celulele Th17 pot avea un rol cheie in scleroza multiplă, de exemplu deoarece nivelurile de IL-17 se pot corela cu leziunile de scleroză multiplă, IL-17 poate întrerupe legăturile strânse ale celulelor endoteliale cu bariera hemato–encefalică şi celulele Th17 pot migra în centrul sistemul nervos şi pot cauza pierderi neuronale [46,47]. Prin urmare, compozițiile conform invenției pot fi deosebit de eficiente pentru prevenirea sau tratarea sclerozei multiple.

In anumite aplicații, tratamentul cu compozițiile conform invenției are ca rezultat o reducere a incidenței bolii sau a severității bolii. În anumite aplicații, compozițiile conform invenției sunt utilizate pentru reducerea incidenței bolii sau a severității bolii. În anumite aplicații, tratamentul cu compozițiile conform invenției previne scăderea funcției motorii sau duce la îmbunătățirea funcției motorii. In anumite aplicații, compozițiile conform invenției sunt utilizate pentru a preveni scăderea funcției motorii sau pentru utilizarea în îmbunătățirea funcției motorii. În anumite aplicații, tratamentul cu compozițiile conform invenției împiedică dezvoltarea paraliziei. În anumite aplicații, compozițiile conform invenției sunt utilizate pentru prevenirea paraliziei în tratamentul sclerozei multiple.

Compozițiile conform invenției pot fi utile pentru modularea sistemului imunitar al pacientului, astfel incat, in anumite aplicații, compozițiile invenției sunt utilizate pentru prevenirea sclerozei multiple la un pacient care a fost identificat ca având risc de scleroză multiplă sau care a fost diagnosticat cu scleroză multiplă în stadiu incipient sau scleroză multiplă „recurentă-remisivă“. Compozițiile conform invenției pot fi utile pentru prevenirea dezvoltării sclerozei.

Compozițiile conform invenției pot fi utile pentru gestionarea sau ameliorarea sclerozei multiple. Compozițiile conform invenției pot fi în mod particular utile pentru reducerea simptomelor asociate cu scleroza multiplă. Tratamentul sau prevenirea sclerozei multiple se poate referi, de

exemplu, la o atenuare a severității simptomelor sau la o reducere a frecvenței exacerbărilor sau a gamei de declanșatoare care reprezintă o problemă pentru pacient.

Moduri de administrare

De preferință, compozițiile conform invenției urmează să fie administrate la nivelul tractului gastrointestinal pentru a permite eliberarea și/sau colonizarea parțială sau totală a intestinului cu tulpina bacteriană a invenției. În general, compozițiile conform invenției sunt administrate pe cale orală, dar pot fi administrate rectal, intranazal sau pe cale bucală sau sublinguală.

In anumite aplicații, compozițiile conform invenției pot fi administrate sub formă de spumă, spray sau gel.

In anumite aplicații, compozițiile conform invenției pot fi administrate sub formă de supozitoare, cum ar fi un supozitor rectal, de exemplu sub formă de ulei de theobroma (unt de cacao), grăsime sintetică tare (de exemplu suppocire, witepsol), glicero-gelatină, polietilen glicol sau compoziție de glicerină de săpun.

In anumite aplicații, compoziția conform invenției este administrată pe tractul gastrointestinal printr-un tub, cum ar fi un tub nasogastric, un tub orogastric, un tub gastric, un tub jejunostomic (tub J), gastrostomia endoscopică percutană (PEG), sau ca un port, cum ar fi portul de perete toracic care oferă acces la stomac, jejun și alte porturi de acces adecvate.

Compozițiile conform invenției pot fi administrate o dată sau pot fi administrate secvențial ca parte a unui regim de tratament. In anumite aplicații, compozițiile conform invenției trebuie administrate zilnic.

In anumite aplicații ale invenției, tratamentul conform invenției este însoțit de evaluarea microbiotei intestinale a pacientului. Tratamentul poate fi repetat dacă nu se realizează administrarea și/sau colonizarea parțială sau totală cu tulpina conform invenției, astfel încât eficacitatea nu este observată sau tratamentul poate fi încetat dacă succesiunea și/sau colonizarea parțială sau totală este de succes și se observă eficacitate.

In anumite aplicații, compoziția conform invenției poate fi administrată la un animal gravid, de exemplu un mamifer cum ar fi un om, pentru a preveni dezvoltarea unei boli inflamatorii sau autoimune la copilul său *in utero* și/sau după naștere.

Compozițiile conform invenției pot fi administrate unui pacient care a fost diagnosticat cu o boală inflamatorie sau autoimună sau care a fost identificat ca prezentând riscul unei boli inflamatorii sau autoimune. Compozițiile pot fi, de asemenea, administrate ca o măsură profilactică pentru a preveni dezvoltarea bolilor inflamatorii sau autoimune la un pacient sănătos.

Compozițiile conform invenției pot fi administrate unui pacient care a fost identificat ca având o microbiotă anormală a intestinului. De exemplu, pacientul poate avea o colonizare redusă sau absentă cu *Erysipelatoclostridium.*

Compozițiile conform invenției pot fi administrate ca un produs alimentar, cum ar fi un supliment nutrițional.

In general, compozițiile conform invenției sunt pentru tratamentul oamenilor, deși pot fi utilizate pentru a trata animale, inclusiv mamifere monogastrice, cum ar fi păsări de curte, porci, pisici, caini, cai sau iepuri. Compozițiile conform invenției pot fi utile pentru îmbunătățirea creșterii și performanței animalelor. Dacă se administrează la animale, se poate utiliza gavajul oral.

Compoziții

In general, compoziția conform invenției cuprinde bacterii. În aplicațiile preferate ale invenției, compoziția este pusă în formulă sub formă crodesicată. De exemplu, compoziția conform invenției poate cuprinde granule sau capsule de gelatină, de exemplu capsule de gelatină tare, care cuprind o tulpină bacteriană conform invenției.

De preferință, compoziția conform invenției cuprinde bacterii liofilizate. Liofilizarea bacteriilor este o procedură bine stabilită și există indicații relevante, de exemplu, în referințele [48–50].

In mod alternativ, compoziția conform invenției poate cuprinde o cultură vie de bacterii active.

In unele aplicații, tulpina bacteriană din compoziția conform invenției nu a fost inactivată, de exemplu, nu a fost inactivată termic. În unele aplicații, tulpina bacteriană din compoziția conform invenției nu a fost omorâtă, de exemplu, nu a fost omorâtă de căldură. În unele aplicații, tulpina bacteriană din compoziția conform invenției nu a fost atenuată, de exemplu, nu a fost atenuată de căldură. De exemplu, în unele aplicații, tulpina bacteriană din compoziția conform invenției nu a fost ucisă, inactivată și/sau atenuată. De exemplu, în unele aplicații, tulpina bacteriană din compoziția invenției este vie. De exemplu, în unele aplicații, tulpina bacteriană din compoziția conform invenției este viabilă. De exemplu, în unele aplicații, tulpina bacteriană din compoziția invenției este capabilă

să colonizeze parțial sau total intestinul. De exemplu, in unele aplicații, tulpina bacteriană din compoziția conform invenției este viabilă și capabilă să colonizeze parțial sau total intestinul.

In unele aplicații, compoziția cuprinde un amestec de tulpini bacteriene vii și tulpini bacteriene care au fost omorate.

In aplicațiile preferate, compoziția conform invenției este încapsulată pentru a permite eliberarea tulpinii bacteriene în intestin. Încapsularea protejează compoziția de degradare până la livrarea la locul țintă, de exemplu prin ruperea cu stimuli chimici sau fizici, cum ar fi presiunea, activitatea enzimatică sau dezintegrarea fizică, care poate fi declanșată de modificări ale pH-ului. Se poate utiliza orice metodă adecvată de încapsulare. Exemplele de tehnici de încapsulare includ capturarea intr-o matrice poroasă, atașarea sau adsorbția pe suprafețe purtătoare solide, autoagregarea prin floculare sau cu agenți de reticulare și izolarea mecanică în spatele unei membrane microporoase sau a unei microcapsule. Inidicații privind încapsularea care pot fi utile pentru prepararea compozițiilor conform invenției sunt disponibile în, de exemplu, în referințele [51] și [52].

Compoziția poate fi administrată pe cale orală și poate fi sub formă de tabletă, capsulă sau pulbere. Produsele incapsulate sunt preferate deoarece *Erysipelatoclostridium ramosum* sunt anaerobe. Alte ingrediente (cum ar fi vitamina C, de exemplu) pot fi incluse ca agenți de absorbție a oxigenului și substraturi prebiotice pentru a îmbunătăți livrarea și/sau colonizarea parțială sau totală și supraviețuirea *in vivo*. In mod alternativ, compoziția probiotică a invenției poate fi administrată pe cale orală ca produs alimentar sau nutrițional, cum ar fi produsul lactat fermentat pe bază de lapte sau pe bază de zer, sau ca produs farmaceutic.

Compoziția poate fi pusă în formulă ca un probiotic.

O compoziție conform invenției include o cantitate eficace terapeutic dintr-o tulpină bacteriană conform invenției. O cantitate eficace terapeutic dintr-o tulpină bacteriană este suficientă pentru a exercita un efect benefic asupra unui pacient. O cantitate eficace terapeutic dintr-o tulpină bacteriană poate fi suficientă pentru a duce la livrarea către intestinul pacientului și/sau colonizarea parțială sau totală a acestuia.

O doză zilnică adecvată de bacterii, de exemplu pentru un om adult, poate fi de la aproximativ 1×10^3 până la aproximativ 1×10^{11} unități de formare a coloniilor (CFU); de exemplu, de la aproximativ 1×10^7 până la aproximativ 1×10^{10} CFU; intr-un alt exemplu de aproximativ 1×10^6 până la aproximativ 1×10^{10} CFU.

In anumite aplicații, compoziția conține tulpina bacteriană într-o cantitate de aproximativ 1×10^6 până la aproximativ 1×10^{11} CFU/g, in raport cu masa compoziției; de exemplu, de la aproximativ 1×10^8 până la aproximativ 1×10^{10} UFC/g. Doza poate fi, de exemplu, de 1 g, 3 g, 5 g și 10 g.

In mod tipic, un probiotic, cum ar fi compoziția conform invenției, este opțional combinat cu cel puțin un compus prebiotic adecvat. Un compus prebiotic este de obicei un carbohidrat nedigerabil, cum ar fi o oligo- sau polizaharidă sau un alcool din zahăr, care nu este degradat sau absorbit în tractul digestiv superior. Prebioticele cunoscute includ produse comerciale precum inulina și transgalacto-oligozaharidele.

In anumite aplicații, compoziția probiotică a prezentei invenții include un compus prebiotic intr-o cantitate de la circa 1 până la circa 30% din masă, față de masa totală a compoziției (de exemplu, de la 5 la 20% din masă). Carbohidrații pot fi selectați din grupul constand din fructo-oligozaharide (sau FOS), fructo-oligozaharide cu catenă scurtă, inulină, izomalt-oligozaharide, pectine, xilo-oligozaharide (sau XOS), chitosan-oligozaharide (sau COS), beta–glucani, amidon modificat și rezistent la guma arabilă, polidextroză, D–tagatoză, fibre de salcâm, carob, ovăz și fibre de citrice. Intr-un aspect, prebioticele sunt fructo-oligozaharidele cu catenă scurtă (pentru simplitate, prezentate mai jos, ca FOSs–c.c); respectivele FOSs–c.c. sunt carbohidrați nedigerabili, in general obținuți prin transformarea zahărului din sfeclă și incluzând o moleculă de zaharoză la care sunt legate trei molecule de glucoză.

Compozițiile conform invenției pot cuprinde excipienți sau purtători acceptabili farmaceutic. Exemple de astfel de excipienți adecvați pot fi găsiți în referința [53]. Purtătorii sau diluanții acceptabili pentru utilizare terapeutică sunt bine cunoscuți în domeniul farmaceutic și sunt descriși, de exemplu, in referința [54]. Exemplele de purtători adecvați includ lactoză, amidon, glucoză, metilceluloză, stearat de magneziu, manitol, sorbitol și alții asemenea. Exemplele de diluanți adecvați includ etanolul, glicerolul și apa. Alegerea purtătorului farmaceutic, a excipientului sau a diluantului poate fi făcută în funcție de calea de administrare dorită și de practica farmaceutică standard. Compozițiile farmaceutice pot cuprinde ca sau în plus față de purtător, excipient sau diluant orice liant adecvat, lubrifiant sau lubrifianți, agent sau agenți de punere în suspensie, agent sau agenți de acoperire, agent sau agenți de solubilizare. Exemplele de lianți adecvați includ amidon, gelatină, zaharuri naturale cum ar fi glucoza, lactoză anhidră, lactoză cu curgere liberă, beta-lactoză, îndulcitori

din porumb, gumă naturală şi sintetică, cum ar fi acacia, tragacantă sau alginat de sodiu, carboximetilceluloză şi polietilenglicol. Exemplele de lubrifianţi adecvaţi includ oleat de sodiu, stearat de sodiu, stearat de magneziu, benzoat de sodiu, acetat de sodiu, clorură de sodiu şi alţii asemenea. În compoziţia farmaceutică pot fi furnizaţi conservanţi, stabilizatori, coloranţi şi chiar agenţi aromatizanţi. Exemplele de conservanţi includ benzoatul de sodiu, acidul sorbic şi esterii acidului p-hidroxibenzoic. Pot fi de asemenea utilizaţi antioxidanţi şi agenţi de suspendare.

Compoziţiile conform invenţiei pot fi puse în formulă ca un produs alimentar. De exemplu, un produs alimentar poate oferi beneficii nutriţionale în plus faţă de efectul terapeutic al invenţiei, cum ar fi un supliment nutriţional. În mod similar, un produs alimentar poate fi pus în formulă pentru a îmbunătăţi gustul compoziţiei conform invenţiei sau pentru a face compoziţia mai atractivă pentru a fi consumată prin faptul că este mai asemănătoare cu un aliment alimentar comun decat cu o compoziţie farmaceutică. În anumite aplicaţii, compoziţia conform invenţiei este pusă în formulă ca un produs pe bază de lapte. Termenul „produs pe bază de lapte“ înseamnă orice produs lichid sau semi-solid pe bază de lapte sau de zer avand un conţinut de grăsimi diferit. Produsul pe bază de lapte poate fi, de exemplu, lapte de vacă, lapte de capră, lapte de oaie, lapte degresat, lapte integral, lapte recombinat din lapte praf şi zer fără prelucrare sau un produs prelucrat cum ar fi iaurt, lapte copt, lapte acru, lapte acru, unt din lapte şi alte produse din lapte acru. Un alt grup important include băuturi din lapte, cum ar fi băuturi din zer, lapte fermentat, lapte condensat, lapte pentru sugari sau bebeluşi; lapte aromatizat, inghetată; alimente care conţin lapte, cum ar fi dulciuri.

In unele aplicaţii, compoziţiile conform invenţiei cuprind una sau mai multe tulpini bacteriene din specia *Erysipelatoclostridium ramosum* şi nu conţin bacterii din nici un alt gen sau care cuprind numai cantităţi minime sau irelevante biologie de bacterii dintr-un alt gen. Astfel, in unele aplicaţii, invenţia furnizează o compoziţie care cuprinde una sau mai multe tulpini bacteriene din specia *Erysipelatoclostridium ramosum,* care nu conţine bacterii din nici un alt gen sau care cuprinde numai cantităţi minime sau irelevante biologic de bacterii dintr-un alt gen, pentru utilizare in tratarea sau prevenirea unei boli inflamatorii sau autoimune.

In anumite aplicaţii, compoziţiile conform invenţiei conţin o singură tulpină sau specie bacteriană şi nu conţin alte tulpini sau specii bacteriene. Astfel de compoziţii pot cuprinde numai cantităţi minime sau irelevante biologic de alte tulpini sau specii bacteriene. Astfel de compoziţii pot fi o cultură care este substanţial liberă de alte specii de organisme. Astfel, în unele aplicaţii, invenţia furnizează o compoziţie care cuprinde o singură tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* care nu conţine bacterii din nici un alt gen sau care cuprinde numai cantităţi minime sau irelevante biologic de bacterii dintr-un alt gen pentru utilizare in tratamentul sau prevenirea unei boli inflamatorii sau autoimune.

In unele aplicaţii, compoziţiile conform invenţiei cuprind mai mult de o tulpină bacteriană. De exemplu, in unele aplicaţii, compoziţiile invenţiei cuprind mai mult de o tulpină din cadrul aceleiaşi specii (de exemplu mai mult de 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 25, 30, 35, 40 sau 45 de tulpini) şi, opţional, nu conţin bacterii din alte specii. In unele aplicaţii, compoziţiile conform invenţiei cuprind mai puţin de 50 de tulpini din aceeaşi specie (de exemplu mai puţin de 45, 40, 35, 30, 25, 20, 15, 12, 10, 9, 8, 7, 6, 5 , 4 sau 3 tulpini) şi, opţional, nu conţin bacterii din alte specii. In unele aplicaţii, compoziţiile conform invenţiei cuprind 1–40, 1–30, 1–20, 1–19, 1–18, 1–15, 1–10, 1–9, 1–8, 1–7, 1–6, 1–5, 1–4, 1–3, 1–2, 2–50, 2–40, 2–30, 2–20, 2–15, 2–10, 2–5, 6–30, 6–15, 16–25 sau 31–50 din aceleaşi specii şi, opţional, nu conţin bacterii din alte specii. În unele aplicaţii, compoziţiile conform invenţiei cuprind mai mult de o specie din acelaşi gen (de exemplu mai mult de 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20 , 23, 25, 30, 35 sau 40 de specii) şi, opţional, nu conţin bacterii din nici un alt gen. In unele aplicaţii, compoziţiile conform invenţiei cuprind mai puţin de 50 de specii din acelaşi gen (de exemplu mai puţin de 50, 45, 40, 35, 30, 25, 20, 15, 12, 10, 8, 7, 6, 5, 4 sau 3 specii) şi, opţional, nu conţin bacterii din nici un alt gen. In unele aplicaţii, compoziţiile conform invenţiei cuprind 1–50, 1–40, 1–30, 1–20, 1–15, 1–10, 1–9, 1–8, 1–7, 1–6, 1–5, 1–4, 1–3, 1–2, 2–50, 2–40, 2–30, 2–20, 2–15, 2–10, 2–5, 6–30, 6–15, 16–25 sau 31–50 de specii din acelaşi gen şi, opţional, nu conţin bacterii din nici un alt gen. Invenţia cuprinde orice combinaţie a celor de mai sus.

In unele aplicaţii, compoziţia cuprinde un consorţiu microbian. De exemplu, în unele aplicaţii, compoziţia cuprinde o tulpină bacteriană de *Erysipelatoclostridium ramosum* ca parte a unui consorţiu microbian. De exemplu, în unele aplicaţii, tulpina bacteriană de *Erysipelatoclostridium ramosum* este prezentă în combinaţie cu una sau mai multe tulpini bacteriene (de exemplu, cel puţin 2, 3, 4, 5, 10, 15 sau 20) din alte genuri cu care poate trăi simbiotic *in vivo* in intestin. De exemplu, in unele aplicaţii, compoziţia cuprinde o tulpină bacteriană de *Erysipelatoclostridium ramosum* in combinaţie cu o tulpină bacteriană dintr-un gen diferit. In unele aplicaţii, consorţiul microbian cuprinde două sau mai multe tulpini bacteriene obţinute dintr-o probă de fecale dintr-un singur

organism, de exemplu un om. In unele aplicații, consorțiul microbian nu este găsit împreună în natură. De exemplu, in unele aplicații, consorțiul microbian cuprinde tulpini bacteriene obținute din probe de fecale din cel puțin două organisme diferite. În unele aplicații, cele două organisme diferite sunt din aceeași specie, de exemplu doi oameni diferiți. În unele aplicații, cele două organisme diferite sunt un copil și un adult umani. În unele aplicații, cele două organisme diferite sunt un mamifer uman și ne-uman.

In unele aplicații, compoziția conform invenției cuprinde suplimentar o tulpină bacteriană care are aceleași caracteristici de siguranță și eficacitate terapeutică ca tulpina MRX027 depusă ca NCIMB 42688, dar care nu este MRX027 depusă ca NCIMB 42688 sau care nu este *Erysipelatoclostridium ramosum* sau care nu este un *Erysipelatoclostridium.*

In unele aplicații, în care compoziția conform invenției cuprinde mai mult de o tulpină, specie sau gen bacterian, tulpinile, speciile sau genurile bacteriene individuale pot fi pentru administrare separată, simultană sau secvențială. De exemplu, compoziția poate cuprinde toate tulpinile, speciile sau genurile bacteriene, sau tulpinile, speciile sau genurile bacteriene pot fi stocate separat și pot fi administrate separat, simultan sau secvențial. În unele aplicații, mai multe tulpini, specii sau genuri bacteriene sunt stocate separat, dar sunt amestecate împreună înainte de utilizare.

In unele aplicații, tulpina bacteriană utilizată în invenție este obținută din fecale de adult uman. In unele aplicații în care compoziția conform invenției cuprinde mai mult de o tulpină bacteriană, toate tulpinile bacteriene sunt obținute din fecale de adult uman sau, dacă sunt prezente alte tulpini bacteriene, ele sunt prezente numai in cantități minime. Bacteriile s-ar putea să fi fost cultivate ulterior obținerii din fecalele de adult uman și utilizate intr-o compoziție conform invenției.

Așa cum s-a menționat mai sus, în unele variante, una sau mai multe tulpini bacteriene de *Erysipelatoclostridium ramosum* este/sunt singurul/singurii agenți activi terapeutic într-o compoziție conform invenției. În unele aplicații, tulpina sau bacteriile bacteriene din compoziție sunt singurii agenți activi terapeutic într-o compoziție conform invenției.

0128] Compozițiile pentru utilizare în conformitate cu invenția pot sau nu să necesite aprobarea de comercializare.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană menționată este liofilizată. În anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană menționată este uscată prin pulverizare. În anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană este liofilizată sau uscată prin pulverizare și în care aceasta este vie. În anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană menționată este uscată prin pulverizare și în care aceasta este viabilă. În anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană este liofilizată sau uscată prin pulverizare și în care aceasta este vie. In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană este liofilizată sau uscată prin pulverizare și în care aceasta este viabilă. În anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană este liofilizată sau uscată prin pulverizare și în care aceasta este capabilă să colonizeze parțial sau total intestinul. In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care tulpina bacteriană este liofilizată sau uscată prin pulverizare și în care aceasta este viabilă și capabilă să colonizeze parțial sau total intestinul.

În unele cazuri, tulpina bacterială liofilizată sau uscată prin pulverizare este reconstituită inainte de administrare. In unele cazuri, reconstituirea se face prin utilizarea unui diluant descris aici.

Compozițiile conform invenției pot cuprinde excipienți, diluanți sau purtători acceptabili farmaceutic.

In anumite aplicații, invenția furnizează o compoziție farmaceutică cuprinzând: o tulpină bacteriană așa cum este utilizată în invenție; și un excipient, purtător sau diluant acceptabil farmaceutic; în care tulpina bacteriană este într-o cantitate suficientă pentru tratarea unei tulburări atunci când este administrată unui subiect care are nevoie de aceasta; și în care tulburarea este selectată din grupul constând din uveită; scleroză multiplă; artrită, cum ar fi artrita reumatoidă, osteoartrita, artrita psoriazică sau artrita juvenilă idiopatică; neuromielită optică (boala Devic); spondilită anchilozantă; spondiloartrită; psoriazis; lupus eritematos sistemic; boală inflamatorie a intestinului, cum ar fi boala Crohn sau colita ulceroasă; boală celiacă; astm, cum ar fi astmul alergic sau astmul neutrofil; boală pulmonară obstructivă cronică (BPOC); sclerită; vasculită; boala lui Behcet; ateroscleroză; dermatită atopică; emfizem; parodontită; rinită alergică; și rejet de alografă.

In anumite aplicații, invenția furnizează o compoziție farmaceutică care cuprinde: o tulpină bacteriană așa cum este utilizată în invenție; și un excipient, purtător sau diluant acceptabil farmaceutic; în care tulpina bacteriană este într-o cantitate suficientă pentru a trata sau preveni o boală

inflamatorie sau autoimună. În aplicațiile preferate, boala sau afecțiunea menționată este selectată din grupul constând din uveită; scleroză multiplă; artrită, cum ar fi artrita reumatoidă, osteoartrita, artrita psoriazică sau artrita juvenilă idiopatică; neuromielită optică (boala Devic); spondilită anchilozantă; spondiloartrită; psoriazis; lupus eritematos sistemic; boală inflamatorie a intestinului, cum ar fi boala Crohn sau colita ulceroasă; boală celiacă; astm, cum ar fi astmul alergic sau astmul neutrofil; boală pulmonară obstructivă cronică (BPOC); sclerită; vasculită; boala lui Behcet; ateroscleroză; dermatită atopică; emfizem; parodontită; rinită alergică; și rejet de alografă.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care cantitatea de tulpină bacteriană este de circa 1×10^3 până la circa 1×10^{11} unități de formare a unităților de colonizare per gram în raport cu masa compoziției.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, in care compoziția este administrată la o doză de 1 g, 3 g, 5 g sau 10 g.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care compoziția este administrată printr-o metodă selectată din grupul constând din cale orală, rectală, subcutanată, nazală, bucală și sublinguală.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, cuprinzând un purtător selectat din grupul constând din lactoză, amidon, glucoză, metilceluloză, stearat de magneziu, manitol și sorbitol.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, care cuprinde un diluant selectat din grupul constand din etanol, glicerol și apă.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, cuprinzand un excipient selectat din grupul constând din amidon, gelatină, glucoză, lactoză anhidră, lactoză cu curgere liberă, beta–lactoză, îndulcitor din porumb, salcâm, tragacantă, alginat de sodiu, carboximetil celuloză, polietilenglicol, oleat de sodiu, stearat de sodiu, stearat de magneziu, benzoat de sodiu, acetat de sodiu și clorură de sodiu.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, cuprinzând în plus cel puțin unul dintre un conservant, un antioxidant și un stabilizator.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, care cuprinde un conservant selectat din grupul constand din benzoat de sodiu, acid sorbic și esteri ai acidului p-hidroxibenzoic.

In anumite aplicații, invenția furnizează compoziția farmaceutică de mai sus, în care atunci cand compoziția este depozitată într-un container etanș la temperatura de circa 4°C sau circa 25°C și recipientul este plasat intr-o atmosferă cu umiditate relativă de 50%, cel puțin 80% din tulpina bacteriană măsurată în unități formatoare de colonii, rămâne după o perioadă de cel puțin circa: 1 lună, 3 luni, 6 luni, 1 an, 1,5 ani, 2 ani, 2,5 ani sau 3 ani.

In unele aplicații, compoziția conform invenției este furnizată într-un recipient etanș, cuprinzand o compoziție așa cum este descrisă aici. În unele aplicații, recipientul etanș este un plic sau o sticlă. În unele aplicații, compoziția conform invenției este furnizată într-o seringă care cuprinde o compoziție așa cum este descrisă aici.

Compoziția din prezenta invenție poate, în unele aplicații, să fie furnizată ca o formulă farmaceutică. De exemplu, compoziția poate fi furnizată ca o tabletă sau o capsulă. În unele aplicații, capsula este o capsulă de gelatină („cap-gel“).

In unele aplicații, compozițiile conform invenției sunt administrate pe cale orală. Administrarea orală poate implica înghițire, astfel încât compusul intră în tractul gastrointestinal, și/sau administrarea bucală, lingual sau sublinguală prin care compusul intră în fluxul sanguin, direct din gură.

Formulele farmaceutice adecvate pentru administrare orală includ dopuri solide, microparticule solide, semi-solide și lichide (incluzând faze multiple sau sisteme dispersate) cum ar fi tablete; capsule moi sau tari care conțin multi- sau nanoparticule, lichide (de exemplu soluții apoase), emulsii sau pulberi; pastile (inclusiv lichide); tablete pentru mestecat; geluri; forme de dozare rapid dispersate; pelicule; ovule; spray-uri; și plasturi bucali/mucoadezivi.

In unele aplicații, formula farmaceutică este o formulă enterică, adică o formulă gastrorezistentă (de exemplu, rezistentă la pH-ul gastric) care este adecvată pentru administrarea compoziției conform invenției în intestin prin administrare orală. Formulele enterice pot fi deosebit de utile atunci când bacteria sau altă componentă a compoziției este sensibilă la acid, de exemplu predispusă la degradare în condiții gastrice.

In unele aplicații, formula enterică cuprinde o acoperire enterică. În unele aplicații, formula este o formă de dozare acoperită enteric. De exemplu, formula poate fi o tabletă acoperită enteric sau o capsulă acoperită enteric sau ceva asemănător. Acoperirea enterică poate fi o acoperire enterică

convenţională, de exemplu o acoperire convenţională pentru o tabletă, o capsulă sau ceva asemănător pentru administrare orală. Formula poate cuprinde o acoperire cu peliculă, de exemplu, un strat de peliculă subţire dintr-un polimer enteric, de exemplu un polimer insolubil in acid.

In unele aplicaţii, formula enterică este intrinsec enterică, de exemplu gastro–rezistentă, fără a fi nevoie de o acoperire enterică. Astfel, în unele aplicaţii, formula este o formulă enterică care nu cuprinde o acoperire enterică. În unele aplicaţii, formula este o capsulă fabricată dintr-un material termogel. In unele aplicaţii, materialul termogel este un material celulozic, cum ar fi metilceluloza, hidroximetilceluloza sau hidroxipropilmetilceluloza (HPMC). In unele aplicaţii, capsula cuprinde o carcasă care nu conţine nici un polimer care formează peliculă. În unele aplicaţii, capsula cuprinde o carcasă şi carcasa cuprinde hidroxipropilmetilceluloză şi nu cuprinde nici un polimer formator de peliculă (de exemplu *vezi* [55]). In unele aplicaţii, formula este o capsulă enterică intrinsecă (de exemplu, Vcaps® de la Capsugel).

In unele aplicaţii, formula este o capsulă moale. Capsulele moi sunt capsule care, datorită adăugărilor de emolienţi, cum ar fi, de exemplu, glicerina, sorbitolul, maltitolul şi polietilenglicolii, prezenţi în carcasa capsulei, pot avea o anumită elasticitate şi moliciune. Capsulele moi pot fi produse, de exemplu, pe bază de gelatină sau amidon. Capsulele moi pe bază de gelatină sunt disponibile comercial de la diverşi furnizori. În funcţie de metoda de administrare, cum ar fi, de exemplu, orală sau rectală, capsulele moi pot avea diferite forme, ele pot fi, de exemplu, rotunde, ovale, alungite sau în formă de torpilă. Capsulele moi pot fi produse prin procedee convenţionale, cum ar fi, de exemplu, prin procesul Scherer, procesul Accogel sau prin procesul de picurare sau de suflare.

Metode de cultivare

Tulpinile bacteriene pentru utilizare in prezenta invenţie pot fi cultivate utilizand tehnici de microbiologie standard, aşa cum este detaliat, de exemplu, în referinţele [56–58].

Mediul solid sau lichid utilizat pentru cultură poate fi agar YCFA sau mediu YCFA. Mediul YCFA poate include (pentru 100 ml, valori aproximative): casitonă (1,0 g), extract de drojdie (0,25 g), $NaHCO_3$ (0,4 g), cisteină (0,1 g), K_2HPO_4 (0,045 g), KH_2PO_4 (0,045 g), NaCI (0,09 g), $(NH_4)_2SO_4$ (0,09 g), $MgS0_4 \cdot 7H_2O$ (0,009 g), $CaCI_2$ (0,009 g), resazurin (0,1 mg), hemin (1 mg), biotină (1 ?g), cobalamină (1 ?g), acid *p*-aminobenzoic (3 ?g), acid folic (5 ?g) şi piridoxamină (15 ?g).

Tulpinile bacteriene pentru utilizarea in compoziţiile de vaccinuri

Inventatorii au găsit că tulpinile bacteriene conform invenţiei sunt utile pentru tratarea sau prevenirea bolilor inflamatorii sau autoimune. Acesta este probabil un rezultat al efectului pe care tulpinile bacteriene conform invenţiei îl au asupra sistemului imunitar al gazdei. Prin urmare, compoziţiile dezvăluite pot fi, de asemenea, utile pentru prevenirea bolilor sau stărilor mediate de calea IL-17 sau Th17, atunci cand sunt administrate ca şi compoziţii de vaccin. În anumite astfel de aplicaţii, tulpinile bacteriene sunt viabile. În anumite aplicaţii, tulpinile bacteriene ale invenţiei sunt capabile să colonizeze parţial sau total intestinul. In anumite aplicaţii, tulpinile bacteriene ale invenţiei sunt viabile şi capabile să colonizeze parţial sau total intestinul. In alte aplicaţii, tulpinile bacteriene ale invenţiei pot fi omorâte, inactivate sau atenuate. În anumite aplicaţii, compoziţiile pot cuprinde un adjuvant al vaccinului. In anumite aplicaţii, compoziţiile sunt pentru administrarea prin injecţie, cum ar fi prin injectare subcutanată.

Generalităţi

Practica prezentei invenţii va folosi, dacă nu este indicat altfel, metode convenţionale de chimie, biochimie, biologie moleculară, imunologie şi farmacologie, în cadrul competenţelor în domeniu. Asemenea tehnici sunt explicate pe deplin în literatură. *Vezi*, de exemplu, referinţele [59] şi [60–66], etc.

Termenul „cuprinzand" include „incluzand" precum şi „constând", de exemplu o compoziţie „cuprinzand" X poate consta exclusiv din X sau poate include ceva suplimentar, de exemplu X + Y.

Termenul „circa" în raport cu o valoare numerică *x* este opţional şi înseamnă, de exemplu, *x*±10%.

Termenul „substanţial" nu exclude „complet", de exemplu o compoziţie care este „substanţial lipsită" de Y poate fi complet lipsită de Y. Dacă este necesar, termenul „substanţial" poate fi omis din definiţia conform invenţiei.

Referinţele la o identitate procentuală de secvenţă între două secvenţe de nucleotide înseamnă că, atunci când sunt aliniate, procentul de nucleotide este acelaşi în comparaţia celor două secvenţe. Această aliniere şi omologia procentuală sau identitatea secvenţei pot fi determinate utiliza nd programe software cunoscute in domeniu, de exemplu cele descrise in secţiunea 7.7.18 din referinţa [67]. O aliniere preferată este determinată de algoritmul de căutare de omologie Smith-Waterman utilizând o căutare a decalajului afinităţii cu o penalizare de deschidere a decalajului de 12

şi o penalizare de extindere a decalajului de 2, matricea BLOSUM 62. Algoritmul de căutare de omologie Smith-Waterman este dezvăluit în referința [68].

Dacă nu se specifică în mod specific altfel, un procedeu sau o metodă cuprinzand numeroase etape poate cuprinde etape suplimentare la inceputul sau la sfarşitul metodei sau poate cuprinde etape intercalate suplimentare. De asemenea, etapele pot fi combinate, omise sau executate intr-o ordine alternativă, dacă este cazul.

Sunt descrise aici diferite aplicații ale invenției. Se va aprecia că caracteristicile specificate in fiecare aplicație pot fi combinate cu alte caracteristici specificate, pentru a furniza alte aplicații. În particular, aplicațiile evidențiate aici ca fiind potrivite, tipice sau preferate pot fi combinate una cu cealaltă (cu excepția cazului în care acestea se exclud reciproc).

Moduri de aplicare a invenției

Exemplul 1 – Eficacitatea inoculului bacterian intr-un model de uveită la şoarece

Rezumat

Acest studiu a utilizat un model de şoarece de uveită indusă de proteina de legare a retinoidului interfotoreceptor (IRBP) pentru a testa efectele administrării bacteriene asupra uveitei. Uveita este o condiție amenințătoare a vederii care rezultă din inflamația intraoculară şi distrugerea tisulară a retinei. Această boală poate fi studiată la rozătoare într-un model de uveoretinită autoimună experimentală (UAE) [69]. EAU este o tulburare specifică organelor în care celulele Th1/Th17 sunt direcționate către antigenii retinieni şi produc citokine care activează celulele mononucleare rezidente şi infiltrate, ducând la distrugerea țesuturilor. EAU poate fi indusă la şoareci prin provocarea cu antigeni retinieni, incluzând peptida proteină de legare a retinoidului interfotoreceptor (IRBPp). Debutul bolii apare in mod normal in ziua 8–9 şi vârfurile după zilele 14–15. Semnele bolii clinice pot fi monitorizate utilizand imagistica endoscopică cu fundal topic (TEFI).

Tulpină

MRX027: *Erysipelatoclostridium ramosum.*

Tulpina folosită în acest exemplu a fost depusă ca NCIMB 42688.

Agentul bioterapeutic a fost furnizat in stoc de glicerol. Mediile de creştere microbiologică (YCFA) au fost utilizate pentru cultura agentului.

Şoareci

Şoarecii au fost din genul C57BL/6 şi au avut vârsta de peste 6 săptămâni la începutul studiului. Au fost utilizaţi 72 de şoareci (+36 de animale satelit). Animalele nesănătoase au fost excluse din studiu. Animalele au fost adăpostite în condiţii specifice lipsite de patogeni (SPF), intr-o încăpere de supraveghere monitorizată termostatic (22 ± 4°C). Animalele au fost lăsate să se aclimatizeze in condiţii normale pentru animalele de casă timp de cel puţin o săptămână înainte de utilizare. Starea de sănătate a animalelor a fost monitorizată pe parcursul acestei perioade şi evaluarea adecvării fiecărui animal pentru utilizarea experimentală a fost efectuată înainte de începerea studiului. Şoarecii au fost adăpostiţi în grupuri de până la 10 animale pe cuşcă pe durata studiului. Dieta pe bază de granule iradiate (dietă Lab, dietă pentru rozătoare EU 22%, 5LF5) şi apă au fost disponibile la discreţie în timpul perioadelor de aclimatizare şi de studiu. Este puţin probabil ca orice constituent al dietei sau apa să interfereze cu studiul.

Descrierea experimentului

Şoarecii adulţi femele C57BL/6 au fost repartizaţi aleatoriu în grupuri experimentale şi au fost lăsaţi să se aclimatizeze timp de o săptămână. Tratamentele au fost administrate conform schemei de mai jos. In ziua 0, animalelor li s-a administrat o emulsie conţinând 200 ?g de peptidă proteină de legare a retinoidului interfotoreceptor 1–20 (IRBP p1–20) in adjuvant Freund complet (CFA) suplimentat cu 2,5 mg/ml *Mycobacterium tuberculosis* H37 Ra prin injectare subcutanată. De asemenea in ziua 0, animalelor li s-au administrat 1,5 ?g de toxină *Bordetella Pertussis* prin injecţie intraperitoneală. Din ziua –14, animalele sunt cântărite de trei ori pe săptămână. De la ziua –1 până la sfarşitul experimentului în Ziua 42, animalele sunt monitorizate de două ori pe săptămână pentru semnele clinice de uveită utilizând imagistică endoscopică cu fundal topic (TEFI).

Program de administrare

Toate grupurile sunt n = 12.

Vehiculul pentru administrare orală este mediu YCFA.

Volumul de administrare pentru administrare orală de două ori pe zi este de 5 ml/kg.

Grup	***Tratament***	***Doză***	***Cale***	***Frecvenţă***	***Inducerea bolilor***
1	*Vehicul*	*5 ml/kg*	*PO*	*BID*	*Ziua 0: IRBP/CFA, SC*
2	*MRX027*	*5 ml/kg*		*Ziua –14–sfarşit*	*Ziua 0: PTx, IP*
PO: administrare orală, BID: de două ori pe zi, SC: injecţie subcutanată, IP: injectare intraperitoneală, IRBP: proteină de legare la interfotoreceptor, CFA: adjuvant Freund complet, PTx: toxină pertussis					

Un grup martor pozitiv a fost, de asemenea, testat utilizand tratamentul cu ciclosporină A.

Citiri

Greutatea corporală. Din ziua –14, animalele sunt cântărite de trei ori pe săptămână. Animalele cu o pierdere în greutate egală sau mai mare de 15% din greutatea lor iniţială (Ziua 0) în două ocazii consecutive sunt sacrificate.

Observaţii clinice nespecifice. Din ziua –14 până la sfârşitul experimentului, animalele sunt verificate zilnic pentru semne clinice nespecifice pentru a include postura anormală (cocoşată), starea anormală a blănii (piloerecţională) şi nivelurile anormale ale activităţii (activitate redusă sau crescută).

Scorurile clinice: Imagistica retiniană prin imagistică endoscopică cu fundal topic (TEFI). Din ziua –1 până la sfârşitul experimentului, animalele sunt marcate de două ori pe săptămână pentru semne clinice de uveită. Imaginile retinale sunt capturate folosind TEFI la animale neanesteziate, dar îngrijite după dilatarea pupilei utilizând tropicamidă 1%, apoi clorhidrat de fenilefrină 2,5%. Imaginile retinale sunt evaluate utilizând următorul sistem. Scorul cumulat maxim este de 20.

Scor	Inflamaţia discului optic	Vasele retinale	Infiltrarea ţesutului retinian	Defecţiuni structurale
1	Minimă	1–4 infiltraţii uşoară	1–4 leziuni mici sau 1 leziune liniară	Leziunile retinei sau atrofia care implică între ? şi ¾ din suprafaţa retinei
2	Blândă	> 4 infiltraţii uşoare	5–10 leziuni mici sau	Atrofie panretinală cu multiple

Scor	Inflamația discului optic	Vasele retinale	Infiltrarea țesutului retinian	Defecțiuni structurale
		sau 1–3 infiltrații moderate	2–3 leziuni liniare	leziuni mici (cicatrici) sau ≤ 3 leziuni liniare (cicatrici)
3	Moderată	> 3 infiltrații moderate	> 10 leziuni mici sau> 3 leziuni liniare	Atrofie panretinală cu > 3 leziuni lineare sau leziuni confluente (cicatrici)
4	Severă	> 1 infiltrație severă	Confluență a leziunii lineare	Detașarea retinei cu pliere
5	Nu este vizibil (eliminare sau detașare severă)			

Rezultate

Rezultatele studiului sunt prezentate in Figurile 1 şi 2.

Scorurile clinice: Imagistica retiniană prin imagistică endoscopică cu fundal topic (TEFI). Datele scorurilor TEFI măsurate în grupul martor de la ziua 0 până la ziua 28 au fost analizate prin testul Kruskal-Wallis pentru date non-parametrice urmate de post-testul Dunn pentru comparații multiple între zilele experimentale.

Administrarea IRBP a indus o creştere semnificativă a scorurilor TEFI măsurate din Ziua 14 ($p < 0,01$) şi în Ziua 28 ($p < 0,0001$) în comparație cu Ziua 0 în grupul Martor (Figura 1).

S-au analizat scorurile TEFI măsurate în grupurile experimentale în Ziua 28 utilizând un ANOVA unidirecțional. După cum era de aşteptat, o scădere semnificativă a scorurilor a fost observată în grupul cu ciclosporină A martor pozitiv. De asemenea, a existat o scădere semnificativă statistic a scorurilor pentru grupul tratat cu MRX027 ($p < 0,05$), comparativ cu martorul negativ (Figura 73).

Concluzii. Scorurile clinice determinate prin TEFI au crescut de la ziua 14, aşa cum se aştepta în acest model de uveită indusă de IRBP. În ziua 28, s-a observat o reducere semnificativă şi statistic semnificativă a incidenței bolii şi a severității bolii în grupul tratat cu MRX027, comparabile cu cele observate pentru grupul martor pozitiv. În special, aceste date indică faptul că tratamentul cu tulpina MRX027 a redus leziunea retinei, inflamația discului optic şi/sau infiltrarea țesutului retinal de către celule inflamatorii (*vezi* sistemul de notare a imaginii retinale TEFI de mai sus). Aceste date indică faptul că tulpina MRX027 poate fi utilă pentru tratarea sau prevenirea uveitei.

Exemplul 2 – Testul de stabilitate

O compoziție descrisă aici care conține cel puțin o tulpină bacteriană descrisă aici este depozitată într-un recipient etanş la temperatura de 25°C sau 4°C şi recipientul este plasat într-o atmosferă având 30%, 40%, 50%, 60%, 70% 75%, 80%, 90% sau 95% umiditate relativă. După 1 lună, 2 luni, 3 luni, 6 luni, 1 an, 1,5 ani, 2 ani, 2,5 ani sau 3 ani, trebuie să rămână cel puțin 50%, 60%, 70%, 80% sau 90% din tulpina bacteriană măsurată în unități de formare a coloniilor determinate prin protocoale standard.

COMPOZIȚII CUPRINZÂND TULPINI BACTERIENE

SEQ ID NO: 1 (rARN 16S al genei *Erysipelatoclostridium (Clostridium) ramosum*, tulpina DSM 1402 – X73440)

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SEQ ID NO: 4 (secvența genomului de *Erysipelatoclostridium ramosum* tulpina DSM 140) – *vezi* SEQ ID NO: 4 publicată în WO 2017/089794

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- NATALYA YUTIN ET AL: "A genomic update on clostridial phylogeny: Gram-negative spore formers and other misplaced clostridia", ENVIRONMENTAL MICROBIOLOGY, 9 July 2013 (2013-07-09), pages n/a-n/a, XP55340305, GB ISSN: 1462-2912, DOI: 10.1111/1462-2920.12173

(57) Revendicări:

1. O compoziţie care cuprinde o tulpină bacteriană din specia *Erysipelatoclostridium ramosum,* pentru utilizare intr-o metodă de tratare sau prevenire a unei boli inflamatorii sau autoimune.

2. Compoziţia pentru utilizare conform revendicării 1, în care compoziţia este destinată utilizării într-o metodă de tratare sau prevenire a unei boli sau stări selectate din grupul constând din uveită; scleroză multiplă; artrită, cum ar fi artrita reumatoidă, osteoartrită, artrita psoriazică sau artrita juvenilă idiopatică; neuromelită optică (boala Devic); spondilită anchilozantă; spondiloartrită; psoriazis; lupus eritematos sistemic; boala inflamatorie a intestinului, cum ar fi boala Crohn sau colita ulceroasă; boală celiacă; astm, cum ar fi astmul alergic sau astmul neutrofil; boală pulmonară obstructivă cronică (BPOC); sclerită; vasculită; boala lui Behcet; ateroscleroză; dermatită atopică; emfizem; parodontită; rinită alergică; şi rejetul de alogrefă.

3. Compoziţia pentru utilizare conform revendicării 2, în care compoziţia este destinată utilizării într-o metodă de tratare sau prevenire a uveitei şi în care compoziţia este destinată utilizării într-o metodă de reducere sau prevenire a leziunii retinei în uveită.

4. Compoziţia pentru utilizare conform revendicării 2, in care compoziţia este destinată utilizării într-o metodă de tratare sau prevenire a astmului, cum ar fi astmul neutrofil sau astmul alergic, şi în care compoziţia este destinată utilizării într-o metodă de reducere a neutrofiliei sau a eozinofiliei in tratamentul astmului.

5. Compoziţia pentru utilizare conform revendicării 2, în care compoziţia este destinată utilizării într-o metodă de tratare sau prevenire a artritei reumatoide şi în care compoziţia este destinată utilizării într-o metodă de reducere a umflării articulaţiilor în artrita reumatoidă.

6. Compoziția pentru utilizare conform revendicării 2, în care compoziția este destinată utilizării într-o metodă de tratare sau prevenire a sclerozei multiple și în care compoziția este destinată utilizării intr-o metodă de reducere a incidenței bolii sau a severității bolii.

7. Compoziția pentru utilizare conform oricăreia dintre revendicările precedente, în care compoziția este destinată utilizării într-o metodă de reducere a producției de IL-17 sau de reducere a diferențierii celulelor Th17 în tratarea sau prevenirea unei boli inflamatorii sau autoimune.

8. Compoziția pentru utilizare conform oricăreia dintre revendicările precedente, în care compoziția este destinată utilizării la un pacient cu niveluri ridicate de IL-17 sau de celule Th17.

9. Compoziția pentru utilizare conform oricăreia dintre revendicările 1–8, in care tulpina bacteriană are o secvență rARN 16S care este cel puțin 95%, 96%, 97%, 98%, 99%, 99,5% sau 99,9% identică cu secvența rARN 16s a unei tulpini bacteriene din specia *Erysipelatoclostridium ramosum* sau SEQ ID NO: 1, 2 sau 3.

10. Compoziția pentru utilizare conform oricăreia dintre revendicările precedente, în care compoziția este pentru administrare orală, în care compoziția cuprinde unul sau mai mulți excipienți sau purtători acceptabili farmaceutic și/sau în care tulpina bacteriană este liofilizată.

11. Compoziția pentru utilizare conform oricăreia dintre revendicările precedente, în care tulpina bacteriană este viabilă și capabilă să colonizeze parțial sau total intestinul.

12. Compoziția pentru utilizare conform oricăreia dintre revendicările precedente, în care compoziția cuprinde o singură tulpină din specia *Erysipelatoclostridium ramosum* și nu conține alte tulpini sau specii bacteriene sau cuprinde numai cantități minime sau irelevante biologic din alte tulpini sau specii bacteriene.

13. Compoziția pentru utilizare conform oricăreia dintre revendicările 1–11, care cuprinde tulpina bacteriană *Erysipelatoclostridium ramosum* ca parte a unui consorțiu microbian, opțional pentru utilizare in terapie.

14. Produs alimentar sau vaccin care cuprinde compoziția conform oricăreia dintre revendicările precedente, pentru utilizare conform oricăreia dintre revendicările precedente.

15. O celulă sau o cultură biologic pură de *Erysipelatoclostridium ramosum* tulpina MRX027 depusă ca NCIMB 42688 pentru utilizare în terapie, opțional în care celula este destinată utilizării intr-o metodă definită în oricare dintre revendicările 1–8.

16. Compoziția cuprinzând celula sau cultura biologic pură pentru utilizare conform revendicării 15, opțional în care compoziția cuprinde un purtător sau excipient acceptabil farmaceutic.

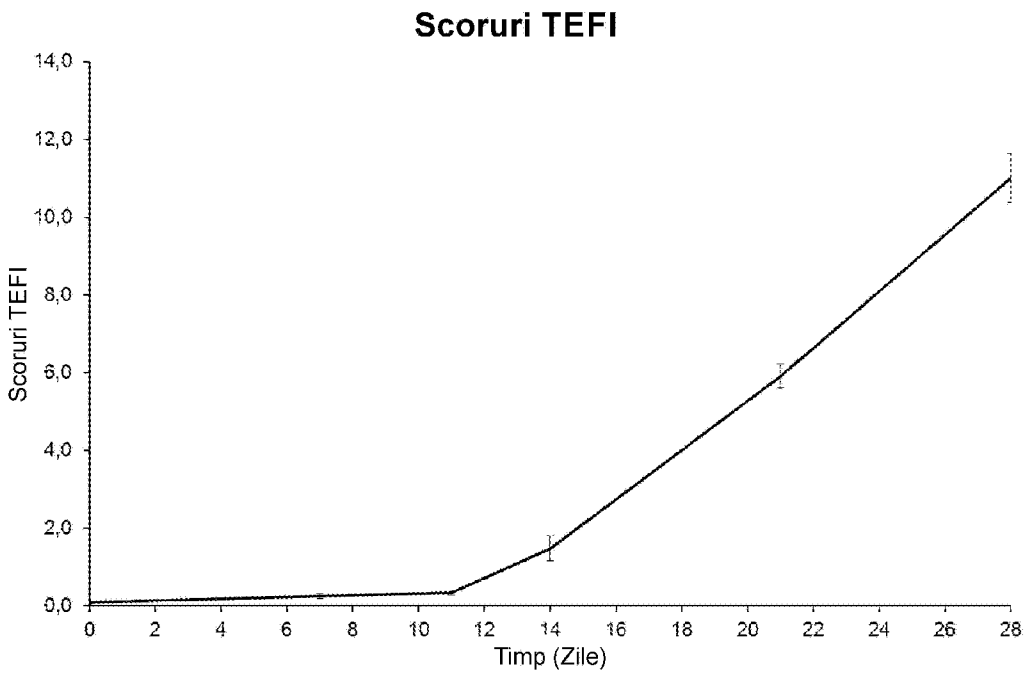

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28
Timp (Zile)

Fig. 1

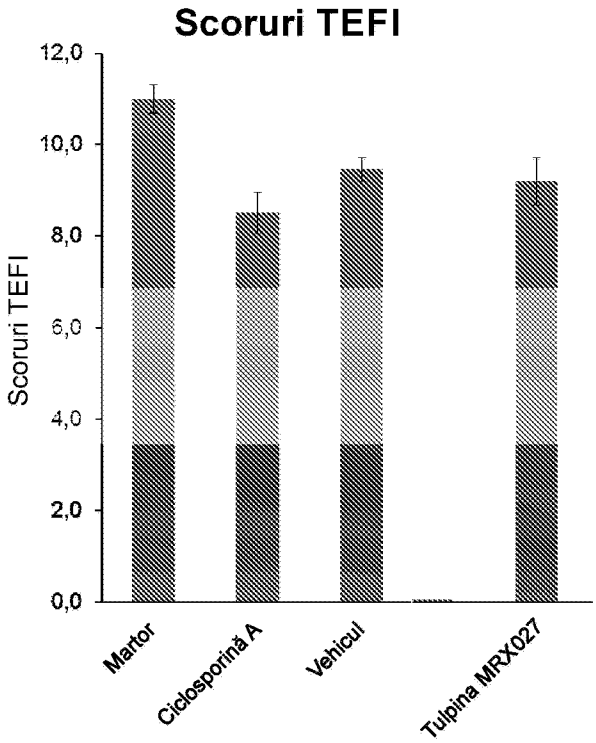

Scoruri TEFI
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Scoruri TEFI
Martor
Ciclosporină A
Vehicul
Tulpina MRX027

Fig. 2