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(54) 발명의 명칭 **항생제 내성을 치료하기 위한 조성물 및 방법**

(57) 요 약

본 발명은 항생제 내성 유전자의 운반을 감소시키기 위한 조성물 및 방법에 관한 것이다.

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명 세 서

청구범위

청구항 1

치료적 유효량의 마이크로바이옴(microbiome) 조성물을 포함하는 조성물로서, 대상체의 마이크로바이옴에서 적어도 하나의 항생제 저항 유전자의 존재비(abundance)를 감소시키는 데 사용하기 위한 포자 형성자 세균(spore-former bacteria)을 포함하는, 조성물.

청구항 2

치료적 유효량의 마이크로바이옴 조성물을 포함하는 조성물로서, 약물 내성 세균의 바람직하지 않은 수준 또는 집단을 가질 위험이 있거나 또는 가지는 것으로 진단된 대상체를 치료하기 위해 사용하기 위한 하나 이상의 건강한 인간 개체로부터 유래된 *후벽균*(*Firmicutes*)을 포함하는, 조성물.

청구항 3

대상체의 마이크로바이옴에서 항생제 내성 세균의 존재비를 감소시키는 용도를 위한 ROAR 조성물.

청구항 4

체액 또는 노폐물과의 선택적 접촉을 포함하여, 직접 또는 간접적으로 접촉할 가능성이 큰 적어도 2 개체에 투여함으로써, 항생제 내성 유전자의 전달 주기를 방해하는 용도를 위한 ROAR 조성물.

청구항 5

제 1 항 또는 제 4 항에 있어서, 상기 항생제 내성 유전자(들)가 표 1에 열거된 것들로부터 선택되는, 조성물.

청구항 6

제 5 항에 있어서, 상기 표 1의 적어도 2, 3, 4, 5, 6, 7, 8, 9, 10개, 또는 그 초과의 항생제 내성 유전자의 존재비가 감소된, 조성물.

청구항 7

제 1 항 내지 제 6 항 중 어느 한 항에 있어서, 상기 약물 또는 항생제가 표 2에 열거된 약물 종류로부터 유래된, 조성물.

청구항 8

제 1 항 내지 제 7 항 중 어느 한 항에 있어서, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25개 또는 그 초과의 항생제 내성 유전자 또는 약물 종류의 존재비를 감소시키는 것을 추가로 포함하는, 조성물.

청구항 9

제 1 항 내지 제 8 항 중 어느 한 항에 있어서, 상기 조성물은 표 3에 열거된 하나 이상의 종을 포함하는, 조성물.

청구항 10

제 9 항에 있어서, 상기 조성물은 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함하는, 조성물.

청구항 11

제 9 항 또는 제 10 항에 있어서, 상기 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는, 조성물.

청구항 12

제 1 항 내지 제 11 항 중 어느 한 항에 있어서, 상기 조성물은 표 4의 하나 이상의 종을 포함하지 않는, 조성물.

청구항 13

제 1 항 내지 제 12 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 포자의 형태인, 조성물.

청구항 14

제 1 항 내지 제 13 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 배양되는, 조성물.

청구항 15

제 1 항 내지 제 14 항 중 어느 한 항에 있어서, 상기 조성물은 *후벽균* 및 하나 이상의 *박테로이데스*(*Bacteroides*) 종을 포함하는, 조성물.

청구항 16

제 1 항 내지 제 15 항 중 어느 한 항에 있어서, 상기 대상체가 퀴놀론 내성, 베타-락탐 내성 및 카바페넴 내성 세균으로 이루어진 군으로부터 선택된 1, 2 또는 3 개의 세균의 감소된 존재비를 갖는, 조성물.

청구항 17

제 1 항 내지 제 16 항 중 어느 한 항에 있어서, 상기 대상체가 항생제 치료에 비반응성이었던, 조성물.

청구항 18

제 1 항 내지 제 17 항 중 어느 한 항에 있어서, 상기 대상체가 *C. 디피실리*(*C.difficile*) 감염되거나 또는 발병할 위험이 있는, 조성물.

청구항 19

제 1 항 내지 제 18 항 중 어느 한 항에 있어서, 상기 대상체가 대장염을 앓거나 또는 발병할 위험이 있는, 조성물.

청구항 20

제 19 항에 있어서, 상기 대장염이 크론병 또는 궤양성 대장염인, 조성물.

청구항 21

제 20 항에 있어서, 상기 대장염이 경증 내지 중등도의 궤양성 대장염인, 조성물.

청구항 22

대상체에서 적어도 하나의 항생제 내성 유전자의 존재비 감소와 관련된 세균 종을 포함하는 조성물.

청구항 23

제 22 항에 있어서, 상기 항생제 내성 유전자(들)가 표 1에 열거된 것들로부터 선택되는, 조성물.

청구항 24

제 23 항에 있어서, 상기 표 1의 적어도 2, 3, 4, 5, 6, 7, 8, 9, 10개 또는 그 초과의 항생제 내성 유전자의 존재비가 감소된, 조성물.

청구항 25

제 22 항 내지 제 24 항 중 어느 한 항에 있어서, 상기 항생제는 표 2에 열거된 종류로부터 유래된, 조성물.

청구항 26

제 22 항 내지 제 25 항 중 어느 한 항에 있어서, 상기 조성물은 표 3에 열거된 하나 이상의 종을 포함하는, 조성물.

청구항 27

제 26 항에 있어서, 상기 조성물은 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함하는, 조성물.

청구항 28

제 20 항 내지 제 27 항 중 어느 한 항에 있어서, 상기 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는, 조성물.

청구항 29

제 22 항 내지 제 28 항 중 어느 한 항에 있어서, 상기 조성물은 표 4의 하나 이상의 종을 포함하지 않고, 선택적으로 표 4의 하나 이상의 종이 표 6에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는, 조성물.

청구항 30

제 22 항 내지 제 29 항 중 어느 한 항에 있어서, 상기 조성물은 하나 이상의 *후벽균* 종을 포함하는, 조성물.

청구항 31

제 22 항 내지 제 30 항 중 어느 한 항에 있어서, 상기 조성물은 하나 이상의 *박테로이데스* 종을 포함하는, 조성물.

청구항 32

제 22 항 내지 제 31 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 포자의 형태인, 조성물.

청구항 33

제 22 항 내지 제 32 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 건강한 대상체의 배설물(feces)로부터 유래된 포자 분획으로부터 수득되는, 조성물.

청구항 34

제 22 항 내지 제 33 항 중 어느 한 항에 있어서, 상기 조성물은 하나 이상의 *후벽균* 종, 및 선택적으로 하나 이상의 *박테로이데스* 종을 조성물 중 유일한 세균 종으로서 포함하는, 조성물.

청구항 35

제 22 항 내지 제 34 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 배양되는, 조성물.

청구항 36

세균을 포함하는 조성물로서, 상기 조성물이 투여되는 대상체에서 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는 용도를 위한 조성물.

청구항 37

제 36 항에 있어서, 상기 조성물 중 세균이 건강한 대상체의 배설물로부터 유래된 포자 분획으로부터 수득되는, 조성물.

청구항 38

제 36 항에 있어서, 상기 세균이 대상체에서 하나 이상의 항생제 내성 유전자의 존재비 감소와 관련되도록 선택

되는, 조성물.

청구항 39

제 36 항 내지 제 38 항 중 어느 한 항에 있어서, 상기 항생제 내성 유전자(들)가 표 1로부터 선택되는, 조성물.

청구항 40

제 36 항 내지 제 39 항 중 어느 한 항에 있어서, 상기 조성물은 표 3에서 선택된 적어도 하나의 종을 포함하는, 조성물.

청구항 41

제 36 항 내지 제 40 항 중 어느 한 항에 있어서, 상기 조성물은 표 4의 종을 포함하지 않는, 조성물.

청구항 42

조성물이 투여되는 대상체에서 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는 데 유용한 세균 조성물을 확인하는 방법으로서, 표 3의 하나 이상의 세균 종의 존재에 대해 상기 조성물을 스크리닝하는 단계를 포함하고, 상기 세균 조성물에서 표 3의 하나 이상의 종의 검출은 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키기 위해 사용될 수 있는 조성물의 확인을 나타내는, 방법.

청구항 43

제 42 항에 있어서, 상기 스크리닝이 상기 조성물 중 표 5의 하나 이상의 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열의 검출을 포함하는 방법.

청구항 44

제 42 항 또는 제 43 항에 있어서, 표 4의 하나 이상의 세균 종의 존재에 대한 스크리닝을 추가로 포함하고, 선택적으로 표 4의 하나 이상의 종은 표 6에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는, 방법.

청구항 45

치료 방법에 사용하기 위해 잠재적 공여자의 배설물을 스크리닝하는 방법으로서, 표 3 또는 표 4의 세균 종의 존재에 대해 잠재적 공여자로부터의 배설물 샘플을 시험하는 단계를 포함하고, 표 3으로부터 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 될 수 있음을 나타내지만, 표 4로부터 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 되지 않아야 함을 나타내는, 방법.

청구항 46

대상체가 ROAR 조성물을 사용하는 치료로부터 이익을 얻을 수 있는지를 결정하는 방법으로서, 상기 대상체로부터의 샘플이 표 4의 하나 이상의 세균 종을 포함하는지를 결정하는 단계를 포함하고, 표 4로부터 하나 이상의 종의 검출은 상기 대상체가 ROAR 조성물을 사용하는 치료로부터 이익을 얻을 수 있다는 점을 나타내는, 방법.

청구항 47

제 22 항 내지 제 41 항 중 어느 한 항에 있어서, 상기 조성물 중의 세균이 항생제 내성의 동물 모델에서 하나 이상의 항생제 내성 유전자(들)의 존재비를 감소시키는 능력을 나타내는, 조성물.

청구항 48

제 47 항에 있어서, 상기 동물 모델은 하나 이상의 항생제로 처리된 후 하나 이상의 항생제 내성 유전자를 보유하는 하나 이상의 세균으로 콜로니화된 마우스를 포함하는, 조성물.

청구항 49

제 48 항에 있어서, 상기 마우스가 반코마이신 내성 세균 또는 반코마이신 및 카바페넴 내성 세균으로 콜로니화

되는, 조성물.

발명의 설명

기 술 분 야

[0001] 본 발명은 항생제 내성 예방 및 치료에 관한 것이다.

배 경 기 술

[0002] 세계 보건 기구 (WHO)에 따르면, 세균의 "항생제 내성은 오늘날 세계 보건, 식량 안보, 및 개발에 대한 가장 큰 위협 중 하나이다" (who.int/mediacentre/factsheets/antibiotic-resistance/en). 항생제 내성은 세균에서 자연적으로 발생할 수 있지만 항생제의 사용 및 오용이 증가함에 따라 크게 악화되고 있다. 문제를 추가하는 것은 항생제 내성 메커니즘의 다양성이다; 다양한 이질적 유전자가 내성을 부여할 수 있고, 관련이 없는 세균이 항생제 내성 유전자를 수평으로 전달할 수 있다. 또한 WHO는 "일부 새로운 항생제가 개발되고 있지만, 이들 중 어느 것도 항생제 내성균의 가장 위험한 형태에 효과가 있을 것으로 예상되지 않는다(같은 글)"고 명시하였다.

[0003] 따라서, 항생제 내성을 감소시키는 새로운 방법이 개발되어 이용 가능하여야 함은 반드시 필수적이다.

발명의 내용

[0004] 본 발명은 세균 조성물이 대상체의 위장 (GI) 마이크로바이옴에서 항생제 내성 유전자의 존재비를 감소시키기 위해 사용될 수 있다는 발견에 관한 것이다.

[0005] 본 발명은 대상체의 마이크로바이옴에서 하나 이상의 항생제 내성 유전자의 존재비를 감소시키는 데 사용하기 위한 포자 형성자 세균을 포함하는 치료적 유효량의 마이크로바이옴 조성물을 포함하는 조성물을 제공한다.

[0006] 본 발명은 또한 바람직하지 않은 수준 또는 집단의 약물 내성 세균을 가질 위험이 있거나 가진 것으로 진단된 대상체를 치료하기 위해 하나 이상의 건강한 인간 개체로부터 유래된 *후벽균*(*Firmicutes*)을 포함하는 치료적 유효량의 마이크로바이옴 조성물을 포함하는 조성물을 제공한다.

[0007] 본 발명은 또한 대상체의 마이크로바이옴에서 항생제 내성 세균의 존재비를 감소시키는 용도를 위한 ROAR 조성물을 제공한다.

[0008] 본 발명은 추가로 선택적으로 체액 또는 노폐물과의 접촉을 포함하는, 직접 또는 간접적으로 접촉할 가능성이 큰 적어도 2명의 개체에 대한 투여를 통해, 항생제 내성 유전자의 전달 주기를 방해하는 용도를 위한 ROAR 조성물을 제공한다.

[0009] 또한, 본 발명은 대상체의 마이크로바이옴의 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는 방법을 제공하며, 상기 방법은 포자-형성자 세균을 함유하는 치료적 유효량의 마이크로바이옴 조성물을 투여하는 것을 포함한다.

[0010] 본 발명은 또한 바람직하지 않은 수준 또는 집단의 약물 내성 세균을 가질 위험이 있거나 가진 것으로 진단된 대상체를 치료하는 방법을 제공하며, 상기 방법은 하나 이상의 건강한 인간 개체로부터 유래된 *후벽균*을 함유하는 치료적 유효량의 마이크로바이옴 조성물을 투여하는 것을 포함한다.

[0011] 본 발명은 추가로 대상체의 마이크로바이옴의 항생제 내성균의 존재비를 감소시키는 방법을 제공하며, 상기 방법은 치료적 유효량의 ROAR 조성물을 투여하는 단계를 포함한다.

[0012] 본 발명은 또한 항생제 내성 유전자의 전달 주기를 방해하는 방법을 제공하며, 상기 방법은 체액 또는 노폐물과의 접촉을 포함하여 직접 또는 간접적으로 접촉할 가능성이 큰 적어도 2 명의 개체에게 ROAR 조성물을 투여하는 단계를 포함한다.

[0013] 상기 언급된 임의의 방법의 다양한 양태는 하기에 제시된 바와 같다.

[0014] 일부 양태에서, 항생제 내성 유전자(들)는 표 1에 열거된 것들로부터 선택된다.

[0015] 일부 양태에서, 표 1의 적어도 2, 3, 4, 5, 6, 7, 8, 9, 10개 또는 그 초과의 항생제 내성 유전자의 존재비가 감소된다.

[0016] 일부 양태에서, 약물 또는 항생제는 표 2에 열거된 약물 종류로부터 유래된다.

[0017] 일부 양태에서, 방법은 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25개 또는 그 초과의 항생제 내성 유전자 또는 약물 종류의 존재비를 감소시키는 단계를 포함하거나 또는 감소시키는 추가적인 결과를 초래하는 용도를 위한 조성물을 추가로 포함한다.

[0018] 일부 양태에서, 조성물은 표 3에 열거된 하나 이상의 종을 포함한다. 일부 양태에서, 표 3에 열거된 종은 또한 표 4에 열거되지 않는다. 조성물은 상기 또는 본원의 다른 곳에 기재된 방법에 의해 투여될 수 있다.

[0019] 일부 양태에서, 조성물은 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함한다. 일부 양태에서, 표 3에 열거된 종은 또한 표 4에 열거되지 않는다. 조성물은 상기 또는 본원의 다른 곳에 기재된 방법에 의해 투여될 수 있다.

[0020] 일부 양태에서, 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함한다. 종은 상기 또는 본원의 다른 곳에 기재된 방법에 의해 투여될 수 있다.

[0021] 일부 양태에서, 조성물은 표 4의 하나 이상의 종을 포함하지 않는다. 일부 양태에서, 포함되지 않은 표 4에 열거된 종은 표 3에 열거되지 않는다. 상기 조성물은 상기 또는 본원의 다른 곳에 기재된 방법에 의해 투여될 수 있다.

[0022] 일부 양태에서, 상기 종은 표 6에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하지 않는다. 종은 상기 또는 본원의 다른 곳에 기재된 방법에 의해 투여될 수 있다.

[0023] 일부 양태에서 조성물 중 세균은 포자의 형태이다.

[0024] 일부 양태에서, 조성물 중 세균은 배양된다.

[0025] 일부 양태에서, 조성물은 *후벽균* 및 하나 이상의 *박테로이데스*(*Bacteroides*) 종을 포함한다.

[0026] 일부 양태에서, 대상체는 퀴놀론 내성, 베타-락탐-내성 및 카바페넴-내성 세균으로 이루어진 군으로부터 선택된 1, 2 또는 3개의 세균의 감소된 존재비를 가진다.

[0027] 일부 양태에서, 대상체는 항생제 치료에 비반응성이었다.

[0028] 일부 양태에서, 대상체는 *C. 디피실리*(*C.difficile*) 감염 또는 질환, 또는 대장염을 앓고 있거나 발병할 위험이 있으며, 일부 양태에서, 대장염은 선택적으로 크론병 또는 궤양성 대장염 (예를 들어, 경증 내지 중등도의 궤양성 대장염)이다. 일부 양태에서, 대상체는 C. 디피실리 감염 또는 질환, 또는 대장염 (예를 들어 크론병 또는 궤양성 대장염, 예를 들어, 경증 내지 중등도의 궤양성 대장염)을 갖지 않는다 (또는 발병 위험이 없다).

[0029] 본 발명은 또한 대상체에서 적어도 하나의 항생제 내성 유전자의 존재비 감소와 관련된 세균 종을 포함하는 조성물을 제공한다.

[0030] 일부 양태에서, 항생제 내성 유전자(들)는 표 1에 열거된 것들로부터 선택된다.

[0031] 일부 양태에서, 표 1의 적어도 2, 3, 4, 5, 6, 7, 8, 9, 10개 또는 그 초과의 항생제 내성 유전자의 존재비가 감소된다.

[0032] 일부 양태에서, 항생제는 표 2에 열거된 종류로부터 유래된다.

[0033] 일부 양태에서, 조성물은 표 3에 열거된 하나 이상의 종을 포함한다. 일부 양태에서, 표 3에 열거된 종은 또한 표 4에 열거되지 않는다.

[0034] 일부 양태에서, 조성물은 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함한다. 일부 양태에서, 표 3에 열거된 종은 또한 표 4에 열거되지 않는다.

[0035] 일부 양태에서, 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함한다.

[0036] 일부 양태에서, 조성물은 표 4의 하나 이상의 종을 포함하지 않는다. 일부 양태에서, 포함되지 않은 표 4의 종은 표 3에 열거되지 않는다.

[0037] 일부 양태에서, 종은 표 6에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하지 않는다.

[0038] 일부 양태에서, 조성물은 하나 이상의 *후벽균* 종을 포함한다.

[0039] 일부 양태에서, 조성물은 하나 이상의 *박테로이데스* 종을 포함한다.

[0040] 일부 양태에서, 조성물 중 세균은 포자의 형태이다.

[0041] 일부 양태에서, 조성물 중 세균은 건강한 대상체의 배설물(feces)로부터 유래된 포자 분획으로부터 수득된다.

[0042] 일부 양태에서, 조성물은 하나 이상의 *후벽균* 종, 및 선택적으로 하나 이상의 *박테로이데스* 종을 조성물 중의 유일한 세균 종으로서 포함한다.

[0043] 일부 양태에서, 조성물 중 세균은 배양된다.

[0044] 본 발명은 또한 조성물이 투여되는 대상체에서 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는 용도를 위한 세균을 포함하는 조성물을 제공한다.

[0045] 일부 양태에서, 조성물 중 세균은 건강한 대상체의 배설물로부터 유래된 포자 분획으로부터 수득된다.

[0046] 일부 양태에서, 세균은 대상체에서 하나 이상의 항생제 내성 유전자의 존재비 감소와 관련되도록 선택된다.

[0047] 일부 양태에서, 항생제 내성 유전자(들)는 표 1로부터 선택된다.

[0048] 일부 양태에서, 조성물은 표 3으로부터 선택된 적어도 하나의 종을 포함한다.

[0049] 일부 양태에서, 조성물은 표 4의 종을 포함하지 않는다.

[0050] 본 발명은 또한 조성물이 투여되는 대상체에서 하나 이상의 항생제 내성 유전자의 존재비를 감소시키는 데 유용한 세균 조성물을 확인하는 방법을 제공하며, 상기 방법은 표 3의 하나 이상의 세균 종의 존재에 대해 조성물을 스크리닝하는 단계를 포함하고, 여기서 세균 조성물에서 표 3의 하나 이상의 종의 검출은 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는데 사용될 수 있는 조성물의 확인을 나타낸다. 일부 양태에서, 표 3의 종은 또한 표 4에 열거되지 않는다.

[0051] 일부 양태에서, 스크리닝은 조성물 중 표 5의 하나 이상의 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열의 검출을 포함한다.

[0052] 일부 양태에서, 방법은 표 4의 하나 이상의 세균 종의 존재에 대한 스크리닝을 추가로 포함한다. 일부 양태에서, 표 4로부터 스크리닝된 종은 또한 표 3에 열거되지 않는다.

[0053] 일부 양태에서, 스크리닝은 조성물 중 표 6의 하나 이상의 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열의 검출을 포함한다.

[0054] 본 발명은 또한 치료 방법에 사용하기 위한 배설물의 공여자를 스크리닝하는 방법을 포함하며, 상기 방법은 표 3 또는 표 4의 세균 종의 존재에 대해 잠재적 공여자로부터의 배설물 샘플을 시험하는 단계를 포함하며, 여기서 표 3으로부터 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 될 수 있음을 나타내는 반면, 표 4로부터 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 되지 않아야 함을 나타낸다. 일부 양태에서, 시험된 표 3으로부터의 종은 표 4에 열거되지 않는다. 일부 양태에서, 시험된 표 4로부터의 종은 표 3에 열거되지 않는다.

[0055] 본 발명은 대상체가 ROAR 조성물로 치료함으로써 이익을 얻을 수 있는지를 결정하는 방법을 추가로 포함하며, 상기 방법은 대상체로부터의 샘플이 표 4로부터의 하나 이상의 세균 종을 포함하는지를 결정하는 것을 포함하며, 여기서 표 4로부터 하나 이상의 종의 검출은 대상체가 ROAR 조성물을 사용하는 치료로부터 이익을 얻을 수 있다는 것을 나타낸다. 일부 양태에서, 시험된 표 3으로부터의 종은 표 4에 열거되지 않는다. 일부 양태에서, 시험된 표 4로부터의 종은 표 3에 열거되지 않는다.

[0056] 본 발명은 조성물 (예를 들어, 상기 및 본원의 다른 곳에 기술된 조성물)을 추가로 제공하며, 여기서 조성물 중 세균은 항생제 내성의 동물 모델에서 하나 이상의 항생제 내성 유전자(들)의 존재비를 감소시키는 능력을 나타낸다. 일부 양태에서, 동물 모델은 하나 이상의 항생제로 처리된 후 하나 이상의 항생제 내성 유전자를 보유하는 하나 이상의 세균으로 콜로니화시킨 마우스이다. 일부 양태에서, 마우스는 반코마이신 내성 세균 또는 반코마이신 및 카바페넴 내성 세균으로 콜로니화된다.

[0057] 본 발명은 또한 본원에 기술된 방법에서 특정된 목적을 위해 본원에 기술된 조성물의 용도, 뿐만 아니라 이들 용도를 위한 약제의 제조를 위한 이들 조성물의 용도를 포함한다.

[0058] 본원에 언급된 각각의 특허 문헌 및 과학 논문, 및 그에 인용된 특허 문헌 및 과학 논문의 전체 개시는, 모든

목적을 위해 본원에 참고로 명백하게 포함된다.

[0059] 본 발명의 추가 특징 및 장점은 하기에 보다 구체적으로 설명된다.

도면의 간단한 설명

[0060] 도 1은 인간 공생 포자 조성물을 투여한 후 7, 28 및 56일에 인간 대상체에서 플루오로퀴놀론 내성과 관련된 유전자의 감소를 검출한 실험 결과를 도시한 그래프이다. 백색 = 위약을 받은 대상체, 중간 회색 = 포자 조성물로 처리된 모든 대상체, 및 어두운 회색 = 유의한 생착 신호를 갖는 대상체의 서브셋으로부터의 결과.

도 2는 인간 공생 포자 조성물을 투여한 후 7, 28 및 56일에 인간 대상체에서 베타-락탐 항생제 내성과 관련된 유전자의 감소를 검출한 실험 결과를 도시한 그래프이다. 백색 = 위약을 받은 대상체, 중간 회색 = 포자 조성물로 처리된 모든 대상체, 어두운 회색 = 유의한 생착 신호를 갖는 대상체의 서브셋으로부터의 결과.

도 3은 코호트 (A: 위약, B: 건강한, 스크리닝된 사람의 대변으로부터 제조된 포자, 매주, D: 반코마이신. 매주 포자 제조, 및 C: 반코마이신, 매일 포자 제조에 의해 패싯화된, 시점 (x 축)에 따라 항생제 내성 유전자의 존재비를 나타내는 그래프이다.

도 4는 빠른 초기 생착을 나타내지 않은 대상체에 비해, 중재군(Arm) D (반코마이신, 매주 포자 제조)에서 포자 제조물에 의해 빠른 초기 생착이 있는 대상체에서 항생제 내성 유전자가 더 빠르게 감소함을 보여주는 그래프이다. 방문 4 (8일)는 항생제 중단 직후이며, 방문 4 (11 일)는 첫 포자 제조 시점이다.

발명을 실시하기 위한 구체적인 내용

[0061] 항생제 내성 (본원에서 "AbxR"으로 지칭함)은 증가하는 전 세계 공중 보건 문제이다. 모든 종류의 항생제에 대한 내성은 전 세계의 모든 지역에서 보고되었으며 (2014, *Antimicrobial Resistance, Global Report on Surveillance, Summary*, WHO) 기존 항생제의 개발은 수요에 비해 상대적으로 느리다. 예를 들어, 1980년대에 리포펩티드 항생제 담토마이신이 발견 이후에 새로운 종류의 항생제는 시판되지 않았다. 또한 항생제 사용을 제한하는 항생제 관리 프로그램은 내성 증가 추세를 즉시 반전시키지 않는다.

[0062] 출원인은 세균, 예를 들어 건강한 인간으로부터 유래된 포자 형성자 세균을 포함하는 조성물로 대상체를 치료하는 것이 인간 대상체에서 AbxR 유전자 (총괄적으로, "장내 레지스톰")의 존재비를 감소시킬 수 있음을 발견하였다. 이러한 조성물은 본원에서 항생제 내성 감소 조성물 (ROAR:reduction of antibiotic resistance 조성물)로 지칭된다.

[0063] 또한, 이러한 치료는 여러 종류의 항생제, 예를 들어, β-락탐 (카바페넴 포함), 퀴놀론, 당펩티드 (예를 들어 반코마이신), 및 테트라사이클린에 대한 내성과 연관된 AbxR 유전자의 존재비를 줄일 수 있다. 또한, 비병원성 공생체는 항생제 내성 유전자를 보유할 수 있으며, 치료는 비병원성 공생 유기체에서 항생제 내성 유전자의 존재비를 감소를 초래하는 것으로 밝혀졌다. 특정 이론을 고수하지 않으면서, 이들 데이터는 비병원성 공생 유기체로부터 병원성 세균으로 항생제 내성 유전자의 수평 이동을 감소시키는 메커니즘에 의해 적어도 부분적으로, 항생제 내성 유전자의 존재를 감소시키는 방법을 지지한다. 이러한 메카니즘은 이들 세균을 영양소에 대한 경쟁에서 우월하게 함으로써 항생제 내성 유전자를 보유하는 세균의 존재비를 감소시키는 것과; AbxR 유전자를 보유하는 잠재적 병원체의 성장을 제한하는 숙주에서의 반응을 유도함으로써 항생제 내성 유전자를 보유하는 세균의 존재비를 감소시키는 것과; AbxR 유전자를 보유한 잠재적 병원체에 직접 길항성인 세균을 도입함으로써 항생제 내성 유전자를 보유하는 세균의 존재비를 감소시키는 것과; 기회 병원체를 감소시키고/시키거나, 항생제 내성 및 감수성 유기체 사이에서 항생제 내성 유전자의 확산 가능성을 감소시키는 것과 적어도 부분적으로 관련될 수 있다. 일부 양태에서, 항생제 내성 유전자의 존재의 감소는 AbxR 유전자를 보유하는 미생물 숙주에서 콜로니화를 감소시킴으로써 발생한다.

[0064] 일부 양태에서, ROAR 조성물은 항생제 내성 전달 주기를 파괴하거나 예방하기 위해 사용된다. 이러한 방법에서, ROAR 조성물은 항생제 내성 주기의 위험이 있는 환경 또는 항생제 내성 주기의 존재가 확인된 환경, 예를 들어 항생제 내성이 퍼지는 것으로 확인되었거나 그러한 퍼질 위험이 있는 환경에 진입하는 대상체에게 투여될 수 있다. 이러한 환경의 예시로는 병원, 중환자실, 요양원, 재활 센터, 그룹 홈 등을 포함한다. 일부 양태에서, 이러한 환경에서의 투여는 만성적이다. 일부 양태에서, 대상체는 하나 이상의 AbxR 유전자에 의한 콜로니화를 예방 또는 감소시키도록 처리된다. 하나 이상의 AbxR 유전자를 보유하는 대상체에서, 대상체가 *C. 디피실리* 질환의 치료 후 이러한 대상체가 항생제 내성 세균에 감염되거나 보유할 수 있기 때문에, 대상체에서

AbxR 감염의 위험을 감소시키고, AbxR 유전자를 전달할 위험을 감소시키는 조성물이 투여될 수 있다. 일부 양태에서, 조성물은 AbxR 유전자의 확산과 관련된 특정 위험이 있는 환경에서 작업자에게 투여된다.

[0065] 일부 환경에서는 예를 들어 병원 (특히 중환자실) 및 요양원에서 환자의 "선택적 오염 제거"가 권장되었다 (예를 들어, Silvestri and van Saene, "Selective decontamination of the digestive tract: an update of the evidence," HSR Proc. Intensive Care Cardiovasc. Anesth. 4:21-29, 2012; Oostdijk et al., "Selective decontamination in European intensive care patients," Intensive Care Med. 38:533-538, 2012 참조). ROAR 조성물은 이들 및 다른 환경에서 항생제 내성 유전자의 존재를 감소시키기 위해 이용 가능한 방법의 설비에 더하여, 이러한 선택적 오염 제거에 유용한 대안 또는 보충일 수 있다.

[0066] *ROAR 조성물*

[0067] ROAR 조성물은 일반적으로 *후벽균*을 포함한다. 일부 양태에서, *후벽균*은 포자를 형성할 수 있다 (포자 형성자). 조성물 중 세균은 포자 형태, 혼합 식물성 및 포자 형태, 또는 식물성 형태일 수 있다. 일부 경우에, 조성물은 *후벽균*으로 이루어진다. 일부 양태에서, ROAR 조성물은 하나 이상의 종의 박테로이데테스(*Bacteroidetes*)를 포함한다. 일부 양태에서, ROAR 조성물은 각각의 *후벽균* 및 *박테로이데테스*로부터의 하나 이상의 종으로 구성된다. 조성물의 단독 세균 종으로서 *후벽균* (또는 후벽균 및 박테로이데테스)을 포함하는 또는 이루어지는 조성물은 자연 발생되지 않는다.

[0068] 비제한적인 예시로서, ROAR 조성물은 대변, 예를 들어 인간 대변으로부터 단리된 세균으로부터 제조될 수 있다. 일반적으로, 대변은 치료될 동물과 동일한 종의 건강한 동물 (예를 들어, 인간)로부터 유래된다. 세균은, 예를 들어, 대변에 존재하는 임의의 비-포자형 세균을 사멸시키기에 적합한 양의 에탄올을 사용하는 방법으로 제조될 수 있다. 이러한 제조의 예시는 예를 들어 WO 2014/121302에서 찾을 수 있다.

[0069] 일부 양태에서, ROAR 조성물은 대상체에서 항생제 내성 유전자의 존재비 감소와 관련된 선택된 세균 종을 포함하거나 이로 구성된다 (예를 들어, 하기 표 3 참조). 이러한 조성물은 본원에서 "설계된 Abx 조성물"로 지칭된다. 설계된 조성물에서 종의 수 (예를 들어, 표 3으로부터)는 예를 들어 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 또는 그 초과일 수 있다. 일부 양태에서, 종의 수는 적어도 하나 및 50 이하, 예를 들어 45 미만, 40 미만, 35 미만, 30 미만, 25 미만, 20 미만, 15 미만, 10 미만, 또는 5 미만일 수 있다. 일부 양태에서, 표 3으로부터 선택된 종은 표 4에 또한 열거된 종을 포함하지 않는다.

[0070] 설계된 ROAR 조성물에서 개별 종을 별도로 배양한 다음 조합하여 조성물을 생성할 수 있다. 일부 양태에서, ROAR 조성물은 조성물의 전부 또는 서브셋을 공-배양한 후 공배양되지 않은 성분을 조합하여 조성물을 생성함으로써 생산된다. 일부 양태에서, ROAR 조성물은 건강한 인간의 배설물로부터 유래된 포자 분획을 배양함으로써 생산된다. 생성된 배양물은 ROAR 조성물로서 사용될 수 있다.

[0071] 일부 양태에서, ROAR 조성물에 포함시키기 위해 선택된 종은 특정 종류의 항생제 내성 유전자, 예를 들어 퀴놀론, 베타-락탐, 및/또는 카바페넴의 존재비의 감소에 대한 내성과 관련된 유전자와 관련이 있다 (또한 표 2 참조). 예를 들어, 상기 기재된 조성물의 특정 예에서, ROAR 조성물 (예를 들어, 설계된 Abx 조성물) 중 세균 종은 표 2로부터 선택되고, 선택적으로는 16S rDNA 서열 (또는 이의 단편, 예를 들어, 16S rDNA V4 및/또는 V6 영역을 포함하는 단편; 또한 예시적 서열에 대해서는 하기 및 표 5 참조)의 분석에 의해 확인될 것이다.

[0072] 일부 양태에서, ROAR 조성물에 유용한 종은 기준 종, 예를 들어 표 3에서 확인된 종의 16S rDNA에 대해 적어도 95%의 서열 동일성 ("동일성") (예를 들어, 적어도 96%, 97%, 98% 또는 99%, 또는 100%)을 갖는 전장 16S rDNA를 갖는 종이다 (예를 들어, 서열 정보는 표 5 참조). 일부 양태에서, ROAR 조성물에 유용한 종은 기준 종, 예를 들어 표 3의 종의 16S rDNA에 대해 적어도 97% 서열 동일성 ("동일성")을 갖는 전장 16S rDNA를 갖는 종이다 (예를 들어, 서열 정보는 표 5를 참조). 일부 양태에서, 유용한 종은 기준 종, 예를 들어 표 3에서 확인된 종의 16S rDNA 서열의 V4 및/또는 V6 영역에 대해 적어도 95% 동일성 (예를 들어, 적어도 96%, 97%, 98%, 또는 99%, 또는 100%)을 갖는 V4 및/또는 V6 영역 16S rDNA 서열을 가진다 (예를 들어, 서열 정보는 표 5 참조). 일부 양태에서, 유용한 종은 기준 종, 예를 들어 표 3에서 확인된 종의 16S rDNA 서열의 V4 및/또는 V6 영역에 대해 적어도 97% 동일성을 갖는 V4 및/또는 V6 영역 16S rDNA 서열을 가진다 (예를 들어, 서열 정보는 표 5를 참조). 일부 양태에서, 유용한 종은 기준 종, 예를 들어 표 3에서 확인된 종의 전장 게놈 DNA에 대해 적어도 95% 동일성 (예를 들어, 적어도 96%, 97%, 98%, 또는 99%, 또는 100%)을 갖는 게놈 서열을 가진다. 일부 양태에서, 유용한 종은 기준 종, 예를 들어 표 3에서 확인된 종의 전장 게놈 서열에 대해 97% 동일성을 갖는 게놈 서열을 가진다. 서열, 예를 들어 16S rDNA, V4 또는 V6 서열이 본원에 제공되지 않는 경우, 이러한 서열을 확

인하기 위한 방법은 당업계에 널리 공지되어 있다. 표 5는 기준 서열로서 사용될 수 있는 전장 16S rDNA 서열의 비제한적 예시를 제공한다. 일반적으로, 기준 종과의 동일성 또는 동일성 백분율은 유기체에서 발견된 하나 이상의 16S rDNA 서열 (또는 단편, 예를 들어 V4 및/또는 V6)과의 동일성 또는 동일성 백분율을 의미한다.

[0073] 일부 경우에, 본 발명에 유용한 세균 종, 예를 들어 본원에 개시된 종의 균주는 ATCC (atcc.org), DSMZ (dsmz.de), 또는 리켄 생물자원 센터 (en.brc.riken.jp)와 같은 공공 생물학적 자원 센터로부터 얻을 수 있다. 본 발명의 종 또는 다른 측면을 확인하는데 유용한 16s rDNA 서열은 공개 데이터베이스, 예를 들어 인간 마이크로바이옴 프로젝트 (HMP) 웹 사이트 또는 GenBank로부터 얻을 수 있다.

[0074] 서열 동일성을 판단하는 방법은 당업계에 공지되어 있으며 예시는 아래에 제공된다.

[0075] 일부 양태에서, ROAR 조성물에서 배제된 종은 특정 종류의 항생제 내성 유전자의 존재와 양의 상관관계가 있는 종이다 (예를 들어, 표 4 참조). 이들 종은 상기 기재된 것과 같은 방법을 사용하여 확인될 수 있다 (또한 상응하는 서열 정보는 표 6 참조).

[0076] 이들 예시에서 "으로 이루어진(consisting of)"은 조성물에 존재하는 세균 유형을 지칭하는 것으로 이해되어야 한다. 그러므로 열거된 종으로 "~으로 이루어진" 세균 제제는 하나 이상의 부형제 (예를 들어, 하나 이상의 캡슐 포함), 수성 또는 비수성 매질 (예를 들어, 글리세롤, 폴리에틸렌 글리콜, 코코아 버터, 물 및/또는 완충제), 및/또는 하나 이상의 프리바이오틱스 또는 소분자 약물과 같은 추가의 비세균성 물질을 함유할 수 있다.

[0077] 종/명명 정보

[0078] 세균의 이름 및 분류는 문헌에 반영되지 않을 수 있는 변경에 따라 달라질 수 있다. 편의상, 일부 세균 종에 대한 대체 명칭이 본원에 제공될 수 있지만 포괄적인 대안 명칭 세트가 되도록 의도되지는 않는다. 일부 양태에서, 종은 16S rDNA 서열의 전부 또는 일부 (예를 들어, V4 또는 V6 영역)의 서열 동일성, 예를 들어 적어도 90%, 93% 95%, 96%, 97%, 98%, 99%, 또는 100% 동일성으로 확인된다.

[0079] 동일성의 결정

[0080] 일부 양태에서, 클레이드, 작동 분류학적 단위 (OTU), 종 및 균주는 이들의 16S rDNA 서열에 의해 식별된다. 클레이드, OTU, 종 및 균주의 관련성은 클레이드, OTU, 종 또는 균주 간의 동일성 백분율에 의해 결정될 수 있다. 기준 서열과 질의 서열(query sequence) 사이의 동일성 백분율은 당업계에 공지된 방법을 사용하여 결정될 수 있다. 이러한 결정을 위한 방법의 비제한적인 예시가 아래에 제공된다. 본원에 사용된 바와 같이, 2개의 뉴클레오티드 서열 사이의 관련성은 파라미터 "동일성"에 의해 기술된다.

[0081] 한 양태에서, 질의 서열과 참조 서열 사이의 서열 동일성의 정도는 (1) 디폴트 스코어링 매트릭스 및 디폴트 갭 페널티를 사용하여 임의의 적절한 정렬 프로그램에 의해 2개의 서열을 정렬하고, (2) 정확한 일치 수를 식별하고, 여기서 정확한 일치는 정렬 프로그램이 정렬에서 주어진 위치에 있는 2개의 정렬된 서열에서 동일한 뉴클레오티드를 확인한 것이며, 그리고 (3) 정확한 일치의 수를 참조 서열의 길이로 나눔으로써 결정된다.

[0082] 또 다른 양태에서, 질의 서열과 참조 서열 사이의 서열 동일성 정도는 (1) 디폴트 스코어링 매트릭스 및 디폴트 갭 페널티를 사용하여 임의의 적절한 정렬 프로그램에 의해 2개의 서열을 정렬하고, (2) 정확한 일치 수를 식별하고, 여기서 정확한 일치는 정렬 프로그램이 정렬에서 주어진 위치에 있는 2개의 정렬된 서열에서 동일한 뉴클레오티드를 확인한 것이며, 그리고 (3) 정확한 일치의 수를 2개의 서열 중 가장 긴 길이로 나눔으로써 결정된다.

[0083] 또 다른 양태에서, 질의 서열과 참조 서열 사이의 서열 동일성의 정도는 (1) 디폴트 스코어링 매트릭스 및 디폴트 갭 페널티를 사용하여 임의의 적절한 정렬 프로그램에 의해 2개의 서열을 정렬하고, (2) 정확한 일치 수를 식별하고, 여기서 정확한 일치는 정렬 프로그램이 정렬에서 주어진 위치에 있는 2개의 정렬된 서열에서 동일한 아미노산 또는 뉴클레오티드를 확인한 위치이며, 그리고 (3) 정확한 일치 수를 "정렬 길이"로 나눔으로써 결정되고, 정렬 길이는 갭 및 서열의 돌출 부분을 포함하는 전체 정렬의 길이이다.

[0084] 서열 동일성 비교는 일반적으로 서열 비교 프로그램의 도움으로 수행된다. 이러한 상업적으로 또는 공개적으로 이용 가능한 컴퓨터 프로그램은 복잡한 비교 알고리즘을 사용하여 둘 이상의 서열 사이의 차이를 초래할 수 있는 진화 사건을 가장 잘 반영하는 둘 이상의 서열을 정렬시킨다. 따라서, 이들 알고리즘은 동일하거나 유사한 아미노산의 정렬을 보상하고 갭의 삽입, 갭 연장 및 비-유사 아미노산의 정렬을 페널티를 주는 스코어링 시스템으로 작동한다. 비교 알고리즘의 스코어링 시스템은 하기를 포함한다:

[0085] i) 갭이 삽입될 때마다 페널티 스코어 할당 (갭 페널티 스코어)

[0086] ii) 기존 갭이 추가 포지션으로 연장될 때마다 페널티 스코어 할당 (연장 페널티 스코어)

[0087] iii) 동일한 아미노산의 정렬시 높은 점수의 할당, 및

[0088] iv) 동일하지 않은 아미노산의 정렬시 가변 점수의 할당.

[0089] 일반적으로, 정렬 프로그램의 디폴트 값은 서열 비교에 사용된다. 동일성을 결정하는데 유용한 적합한 컴퓨터 프로그램은 예를 들어 BLAST (blast.ncbi.nlm.nih.gov)를 포함한다.

[0090] 본 발명의 한 양태에서, 정렬 프로그램은 선택된 서열의 전장, 예를 들어 전장, V4 또는 V6 16S rDNA 서열에 대한 정렬을 최적화한다. 예를 들어, 전체 정렬 프로그램은 니들만 브니쉬 (Needleman-Wunsch) 알고리즘 (Needleman and Wunsch, J. Mol. Biol. 48: 443-453, 1970)을 기반으로 한다. 이러한 프로그램의 비제한적인 예시는 ebi.ac.uk/Tools/psa/에서 사용 가능한 EMBOSS 니들 및 EMBOSS 스트레쳐 프로그램이다.

[0091] 한 양태에서, 서열은 전체 정렬 프로그램에 의해 정렬되고, 서열 동일성은 프로그램에 의해 식별된 정확한 일치의 수를 "정렬 길이"로 나눈 값을 식별함으로써 계산되며, 여기서 정렬 길이는 서열의 갭과 돌출 부분을 포함하는 전체 정렬의 길이이다. 다른 실시예에서, 전체 정렬 프로그램은 니들만 브니쉬 알고리즘을 사용하고, 서열 식별은 프로그램에 의해 식별된 정확한 일치의 수를 "정렬 길이"로 나눈 값을 식별함으로써 계산되며, 여기서 정렬 길이는 서열의 갭 및 돌출 부분을 포함하는 정렬 전체의 길이이다.

[0092] 또 다른 양태에서, 전체 정렬 프로그램은 EMBOSS 니들 및 EMBOSS 스트레쳐로 구성된 군으로부터 선택되고, 서열 식별은 프로그램에 의해 식별된 정확한 일치의 수를 "정렬 길이"로 나눈 값을 식별함으로써 계산되며, 여기서 정렬 길이는 갭 및 서열의 돌출 부분을 포함하는 전체 정렬의 길이이다.

[0093] 소프트웨어가 정렬을 생성하면, 유사성 백분율(%)과 서열 동일성 백분율(%)을 계산할 수 있다.

[0094] *AbxR 활성 또는 AbxR 유전자의 존재에 대해 조성물을 시험하는 방법*

[0095] ROAR 조성물은 당 업계에 공지된 시험관 내 및/또는 생체 내 모델을 이용하여 동물의 위장관에서 항생제 내성 유전자의 존재비를 감소시키는 능력에 대해 시험될 수 있다 (예를 들어, Schjørring and Krogfelt, Int. J. Microbiol. 2011:312956, 2011; Marra, "Animal models in drug development for MRSA," Meth. Mol. Biol. 1085:333-345, 2014 참조). 이러한 모델은 후보 ROAR 조성물을 시험하는 데 사용하기에 적합할 수 있다. 적합한 모델의 추가 예시는 실시예에 기재되어 있다. 또한, ROAR 조성물은 임상 시험에 등록된 인간 대상체에서 AbxR 유전자의 존재비를 감소시키는 능력에 대해 시험될 수 있다.

[0096] *대상체*

[0097] 일부 양태에서, 본원에 개시된 조성물 (ROAR 조성물)을 사용하여 치료하기에 적합한 대상체는 예를 들어 위장 (GI) 관의 적어도 일부에서, 바람직하지 않은 수준의 AbxR 미생물을 가질 위험이 있거나 진단된 동물, 예를 들어, 포유류, 예를 들어, 인간, 개, 고양이, 소, 양과, 염소, 말, 또는 다른 농장, 가축 또는 동물원 동물이다. 바람직하지 않은 수준의 AbxR 유기체는 예를 들어, 인간을 치료하는 맥락에서, 건강한 집단, 인간 마이크로바이옴 프로젝트 데이터베이스에 기록된 건강한 집단에서의 것보다 상당히 높은 수준으로 식별될 수 있다. 이러한 유기체는, 예를 들어, 대상체로부터 대변 또는 다른 위장 샘플을 배양하고 항생제 내성의 존재에 대한 공지된 시험 방법을 사용하여 검출될 수 있다. 방법은 예를 들어, 희석 방법 (배지 한천 희석법), 디스크-확산법, E-테스트, 자동화 방법, 베타-락타마제 검출 시험 및 발색 세팔로스포린 시험과 같은 메커니즘 특정 시험, PCR 및 DNA 혼성화법과 같은 유전자형 분석법을 포함한다. 이러한 방법은 또한 전체 범유전체학 샷건 (whole metagenomics shotgun, WMS) 시퀀싱에 의한 항생제 내성 관련 유전자의 확인 및 정량을 포함한다. 일부 양태에서, AbxR 유기체 또는 유전자의 바람직하지 않은 수준은 AbxR의 표현형과 관련된 유전자, 유전자 카세트 또는 유전자 마커의 존재 또는 부재를 확인하는 분자생물학적 방법을 사용하여 식별될 수 있다. 이러한 분자생물학적 방법의 일부 예시는 DNA 시퀀싱, 전사 프로파일링 및 분자 프로브를 이용하는 방법을 포함하지만 이에 제한되지 않는다.

[0098] 일부 양태에서, ROAR 조성물로 치료하기에 적합한 대상체는 하나 이상의 항생제로의 치료에 반응하거나 반응하지 않았으며, 항생제 내성 미생물 집단의 존재가 유추된다.

[0099] 일부 양태에서, ROAR 조성물로 치료하기에 적합한 대상체는 *C. 디피실리* 감염 또는 질환이 있거나 발병할 위험이 있다. 일부 양태에서, ROAR 조성물로 치료하기에 적합한 대상체는 대장염 (예를 들어, 크론병 또는 궤양성

대장염 (예를 들어, 경증 내지 중등도의 궤양성 대장염))을 갖거나 발병할 위험이 있다.

[0100] **이점**

[0101] 대상체의 마이크로바이옴에 의한 항생제 내성의 존재 또는 발달 가능성에 더하여, 종래의 항생제의 사용은 예를 들어 장내 세균 불균형, 병원체의 과다 증식, 신경계 손상 및 알레르기 반응과 같은 GI 효과를 포함하는 심각한 부작용을 유발할 수 있다. ROAR 조성물은 전형적으로 공생 세균을 포함하고 예를 들어 치료를 받는 대상체에 의해 내약성이 우수한, 제한된 부작용을 가진다. ROAR 조성물은 필요에 따라, 시간이 지남에 따라 반복적으로 투여될 수 있고, 예를 들어, 치료된 개체에서 항생제 내성 유전자의 유병률을 감소시킴으로써, 다수의 항생제군에 항생제 내성이 발생할 위험을 감소시킬 수 있다. 일반적으로, ROAR 조성물은 세균이 항생제 내성 유전자를 전달하는 전달주기를 조절할 수 있다. 이 특징은 예를 들어, 조성물의 사용이 취약한 환자가 개별적으로 및 환자 집단으로 둘 모두로서 항생제 내성에 노출되거나 항생제 내성에 걸릴 위험을 감소시키는 의료 환경에서 유용하다.

[0102] 일부 양태에서, 조성물의 투여가 예를 들어, 국소 염증의 양을 감소시키고, GI 국소 미생물에 의한 전위 및 감염의 위험을 감소시킴으로써 상피 및 점막 장벽의 완전성을 개선시킬 수 있는 ROAR 조성물의 추가 이점이 있다.

[0103] **정의**

[0104] 세균의 유형, 예를 들어 종의 "증강(augmentation)"은 존재비의 비모수적 시험에 의해 조성물에 존재하지 않는 종의 증가된 존재비의 처리 후 검출을 특징으로 하는 본 발명의 조성물로의 처리 효과이다.

[0105] 세균의 유형, 예를 들어 종의 "생착(engraftment)"은 투여된 조성물로부터 종의 처리 후 검출을 특징으로 하는 본 발명의 조성물로의 처리 효과이며, 이는 처리된 대상체 전처리에서 검출되지 않는다. 검출 방법은 당업계에 공지되어 있다. 한 예시에서, 방법은 PCR에 대한 표준 파라미터를 사용하는 16S rDNA 서열의 PCR 검출이다.

[0106] "작동 분류학 단위(Operational taxonomic unit)", "OTU" (또는 복수, "OTUs")는 계통 발생 수의 말단 잎을 말하며 핵산 서열, 예를 들어 종의 수준에서 이러한 핵산 서열에 대해 서열 동일성을 공유하는 전체 게놈, 또는 특정 유전자 서열, 및 모든 서열에 의해 정의된다. 일부 양태에서 특정 유전자 서열은 16S 서열 또는 16S 서열의 일부, 예를 들어 가변 영역, 예를 들어, V4 영역이다. 다른 양태에서, 두 독립체의 전체 게놈을 시퀀싱하고 비교한다. 다른 양태에서, 다중 위치 서열 태그 (multilocus sequence tags, MLST), 특정 유전자 또는 유전자들의 집합과 같은 선택 영역을 일반적으로 비교한다. 16S 양태에서, 전체 16S 또는 16S 서열의 가변 영역에 걸쳐 ≥97% 평균 뉴클레오티드 동일성을 공유하는 OTU는 동일한 OTU로 간주된다 (예를 들어, Claesson et al., Nucleic Acids Res. 38:e200, 2010; Konstantinidis et al., Philos. Trans. R. Soc. Lond. B. Biol. Sci. 361:1929-1940, 2006 참조). 완전한 게놈, MLSTs, 특정 유전자, 또는 유전자 세트를 포함하는 양태에서, ≥95% 평균 뉴클레오티드 동일성을 공유하는 OTU는 동일한 OTU로 간주된다 (예를 들어, Achtman and Wagner, Nat. Rev. Microbiol. 6:431-440, 2008 참조). 일부 양태에서, 유기체 간의 서열을 비교함으로써 OTU를 구별할 수 있다. 일반적으로, 95% 미만의 서열 동일성을 갖는 서열은 동일한 OTU의 일부를 형성하는 것으로 간주되지 않는다. OTU는 또한 뉴클레오티드 마커 또는 유전자의 임의의 조합, 특히 고도로 보존된 유전자 (예를 들어, "하우스-키핑" 유전자), 또는 이들의 조합에 의해 특징지어질 수 있다. 이러한 특성화는 예를 들어 WGS 데이터 또는 전체 게놈 서열을 사용한다. 본원에 사용된 용어 "종(species)" 및 "OTU"는 문맥에 의해 달리 구별되지 않는 한 상호 교환적으로 사용된다.

[0107] 본원에 기술된 조성물의 "치료적 유효량"은 개체의 질환 상태, 연령, 성별 및 체중과 같은 인자, 및 개체에서 원하는 반응, 예를 들어 하나 이상의 장애 파라미터의 완화, 또는 장애의 하나 이상의 증상의 완화 (및 선택적으로, 투여되는 임의의 추가 작용제의 효과)를 유도하는 조성물의 능력에 따라 달라질 수 있다. 치료적 유효량은 또한 조성물의 임의의 독성 또는 유해 효과가 치료학적으로 유리한 효과보다 더 큰 양이다. 본원에 기재된 바와 같은 조성물은 일반적으로 치료적 유효량으로 투여된다.

[0108] **제제(formulation)**

[0109] 본원에 기재된 ROAR 조성물 (예를 들어, 설계된 Abx 조성물)은 당 업계에 공지된 방법을 사용하여 제조 및 투여될 수 있다. 임의의 적절한 방법이 사용될 수 있지만, 일반적으로, 조성물은 경구, 결장 내시경 또는 비위 전달용으로 제제화된다.

[0110] ROAR 제제는 이러한 제제의 제조 또는 전달에 적합한 하나 이상의 약제학적 부형제를 함유할 수 있다. 일부 양태에서, 제제는 액체 제제이다. 일부 양태에서, ROAR 조성물을 포함하는 제제는 하나 이상의 계면 활성제, 보

조제, 완충제, 산화방지제, 등장성 조절제, 증점제, 점도 조절제 등을 포함할 수 있다.

[0111] 일부 양태에서, 치료는 약제학적으로 허용가능한 담체를 포함하는 제제로 ROAR 조성물을 투여하는 것을 포함한다. 일부 양태에서, 부형제는 ROAR 조성물을 경구 투여 형태로 제공하기에 적합한 캡슐 또는 다른 형식을 포함한다. 부형제가 희석제로서 작용할 경우, 이는 활성 성분에 대한 비히클, 담체, 또는 매질로서 작용하는 고체, 반고체, 또는 액체 물질이 될 수 있다. 따라서, 제제는 정제, 환제, 산제, 로젠지제, 사쉐, 카세제, 엘릭시르제, 현탁제, 유제, 용액제, 시럽제, 연질 또는 경질 캡슐제, 좌제 또는 포장된 분말의 형태일 수 있다.

[0112] 적합한 부형제의 일부 예시는 락토오스, 덱스트로스, 수크로스, 소르비톨, 만니톨, 전분, 검 아카시아, 인산칼슘, 알기네이트, 트라가칸트, 젤라틴, 칼슘 실리케이트, 미세결정질 셀룰로스, 폴리비닐피롤리돈, 셀룰로오스, 물, 시럽, 폴리에틸렌 글리콜, 글리세롤 및 메틸 셀룰로오스를 포함한다. 조성물은 당업계에 공지된 절차를 이용하여 환자에게 투여된 후 활성 성분을 빠르게, 지속하여, 또는 지연 방출로 제공하기 위해 제제화될 수 있다.

[0113] ROAR 조성물은 단위 투여 형태로 제제화될 수 있다. 일반적으로, 투여량은 약 10e2 내지 10e9 생존 가능한 콜로니 형성 단위 (cfu)를 포함한다. 일부 양태에서, ROAR 조성물은 포자 형태의 포자 형성 세균을 포함하거나 포자 형성 세균으로 구성된다. 이러한 경우에, 투여량은 "포자 CFU" 또는 "sCFU"로 결정될 수 있으며, 이는 전형적으로 플레이트 상에서 발아 및 성장에 의해 생존 가능한 포자의 수를 정량화한다.

[0114] 용어 "단위 투약 형태"는 인간 대상체 및/또는 다른 포유동물에 대한 단위 투여량으로서 적합한 물리적 이산 단위를 지칭하며, 각 단위는 적합한 제약 부형제와 관련하여 원하는 치료 효과를 생성하도록 계산된 미리 결정된 양의 활성 물질을 함유한다. 투여량은 다수의 전달 비히클, 예를 들어 다수의 환제 또는 캡슐로 투여될 수 있다.

[0115] ROAR 조성물을 환자에게 투여하는 양 및 빈도는 투여되는 것, 투여의 목적, 예를 들어 예방 또는 치료, 환자의 상태, 투여 방식 등에 따라 달라질 것이다. 치료적 적용에서, 조성물은 질환의 하나 이상의 증상 또는 그의 합병증을 치료 또는 적어도 부분적으로 정지시키기에 충분한 양으로 질환을 앓고 있는 환자에게 투여될 수 있다. 유효 복용량은 질환이나 치료될 병태, 뿐만 아니라 담당 임상의의 판단에 의해, 질환의 중증도, 나이, 체중, 환자의 일반적인 상태 등과 같은 인자에 따라 다를 수 있다.

[0116] 투여량은 예를 들어, 각각의 개별 종 또는 균주의 cfu의 총 수를 참조할 수 있거나, 투여량에서 미생물의 총 수를 참조할 수 있다. 당업계에서 투여량에서 유기체의 수를 결정하는 것은 정확하지 않으며 존재하는 유기체의 수를 결정하는데 사용된 방법에 의존할 수 있는 것으로 이해된다. 예를 들어, 조성물 중 포자의 수는 디피콜린산 분석을 사용하여 결정될 수 있다. 일부 경우에, 유기체의 수는 배양 분석을 사용하여 결정될 수 있다. 포자가 존재할 때, 배양 방법에 의존하는 분석의 능력은 포자의 효율적인 발아에 의존할 수 있다. 정량적 핵산-기반 방법은 비-생존 미생물로부터의 핵산이 충분히 감소 또는 제거되는지에 의존할 수 있다. 시험관 내 또는 동물 모델 시험 시스템으로부터 유도된 용량-반응 곡선으로부터 유효 복용량을 추정할 수 있다.

[0117] **스크리닝 방법**

[0118] 본 발명은 또한 대상체에서 항생제 내성 유전자의 존재비를 감소시키기 위해 사용될 수 있는 세균 조성물을 확인하는 방법을 제공한다. 이들 방법에서, 후보 조성물은 표 3의 하나 이상의 세균 종의 존재에 대해 분석된다. 이들 종의 하나 이상의 검출 (예를 들어, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 또는 그 초과)은 조성물이 항생제 내성 유전자의 존재비를 감소시키는 데 유용할 수 있음을 나타낸다. 후보 조성물을 추가로 스크리닝하기 위해 추가 시험을 수행할 수 있다. 예를 들어, 후보 조성물은 표 4의 하나 이상의 종의 존재에 대해 추가로 분석될 수 있다. 일부 양태에서, 표 4의 하나 이상의 (예를 들어, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 또는 그 초과)의 종을 포함하는 것으로 확인된 조성물의 사용을 피하는 것이 바람직하다고 결정할 수 있다.

[0119] 본 발명의 다른 스크리닝 방법에서, 치료 방법 (예를 들어, 본 발명의 치료 방법)에 사용하기 위한 배설물의 잠재적 공여자는 공여자로서의 역할에 적합한지 스크리닝된다. 이들 방법에서, 잠재적 공여자의 배설물 샘플은 감소된 항생제 내성 유전자와 관련된 하나 이상의 세균 종 (예를 들어, 표 3 참조; 서열은 표 5 참조) 및/또는 항생제 내성 유전자의 존재와 상관관계가 있는 하나 이상의 세균 종 (예를 들어, 표 4 참조; 서열은 표 6 참조)의 존재에 대해 스크리닝된다. 전자의 검출은 잠재적 공여자가 공여자로서의 역할을 수행하기에 적합하다는 것을 나타낼 수 있는 반면, 후자의 검출은 잠재적 공여자가 당업자에게 결정될 수 있는 바와 같이, 잠재적 공여자가 진행되지 않아야 한다는 것을 나타낼 수 있다.

[0120] 추가의 스크리닝 방법은 본원에 기재된 바와 같이, 대상체가 ROAR 조성물로 치료할 수 있는지를 결정하는데 사

용되는 방법을 포함한다. 이들 방법에서, 대상체로부터의 샘플 (예를 들어, 배설물 샘플)은 항생제 내성 유전자의 존재와 상관된 하나 이상의 세균 종의 존재에 대해 시험된다 (예를 들어, 표 4 및 6 참조). 이들 종 중 하나 이상의 검출은 대상이 당업자에 의해 결정될 수 있는 바와 같이, 본 발명의 치료 방법에 따른 치료로부터 이익을 얻을 수 있음을 나타낼 수 있다.

[0121] 본 발명의 이들 방법에서 종의 검출은 당업계에 공지된 방법을 사용하여 수행될 수 있다 (예를 들어, 상기 및 본원의 다른 곳 참조). 예를 들어, qPCR, 전체 범유전체학 샷건 시퀀싱 (WMS; 예를 들어 이하 참조), 및/또는 16S rDNA 서열 또는 그의 일부의 분석 (예를 들어, V4 및/또는 V6 영역; 예를 들어, 표 5)을 포함하는 방법이 수행될 수 있다. 표 5로부터의 서열은 음의 상관관계의 확인 (즉, 항생제 내성 유전자의 감소)과 관련하여 검출될 수 있다. 표 6으로부터의 서열은 양의 상관관계의 확인 (즉, 증가된 항생제 내성 유전자의 존재비)과 관련하여 검출될 수 있다.

[0122] **등가물**

[0123] 모든 기술적 특성은 이러한 특성의 가능한 모든 조합으로 개별적으로 결합될 수 있다.

[0124] 본 발명은 이의 사상 또는 본질적인 특성을 벗어나지 않으면서 다른 특정 형태로 구현될 수 있다. 그러므로 전술한 양태는 모든 면에서 본 명세서에 기술된 본 발명을 제한하기보다는 예시적인 것으로 간주되어야 한다.

[0125] **실시예**

[0126] 하기 비제한적인 예시는 본원에 기재된 본 발명의 양태를 추가로 설명한다.

[0127] 실시예 1: 인간 연구 - *클로스트리듐 디피실리(Clostridium difficile)*

[0128] 재발성 *클로스트리듐 디피실리* 감염 (rCDI)의 위험이 있는 인간 대상체를 무작위, 이중 맹검, 위약-대조 2상 시험 (n=89; 무작위화 2:1; 36개 장소)에서 건강한 스크리닝된 인간의 대변으로부터 제조된 강화되고(enriched) 정제된 포자로 처리하였다. 포자를 단일 용량 (4 캡슐)으로 경구 투여하였다. 투약량은 10e8 포자 당량이었다. 이들 대상체의 GI 마이크로바이옴 뿐만 아니라 1b 상 개방 표지 용량 범위 연구에서 대상체는 전체 범유전체학 샷건 시퀀싱 (WMS)을 사용하여 프로파일링하였다. 대변 샘플을 포자로 처리하기 전 (항생제로 처리한 후) 및 적용 가능한 경우, 포자 또는 위약을 투여받은 후에 수집하였다.

[0129] 대변 샘플에서 DNA를 추출하고 일루미나 시퀀싱 플랫폼을 WMS 데이터를 생성하는 데 사용하였다. WMS 데이터는 포괄적 항생제 내성 데이터베이스 (CARD v.1.1.8) (card.mcmaster.ca)에 기재된 바와 같이, 항생제 내성을 부여하는 것으로 알려진 단백질의 유전자 마커의 존재(presence) 및 존재비(abundance)에 대해 스크리닝하였다. 이들 단백질과 관련된 유전자 마커는 ShortBRED (Kaminski et al., PLoS Comput Biol 11 (12): e1004557), WMS 데이터 내에서 높은 특이성으로 관심있는 단백질을 확인하도록 설계된 정보 도구를 사용하여 구축하였다 (표 1). 각 종류의 항생제에 대해, 해당 종류에 대한 내성과 관련된 유전자 마커의 존재비는 정규화된 유전자 존재비 값을 생성하는 것으로 합산하였다 (본원에서 약물 종류 마커 존재비 또는 DCMA로 지칭됨).

[0130] 2상 연구를 위해, WMS 분석을 기반으로 포자 형성 종의 차별 유병률을 관찰하였다. ARDB에서 확인된 항생제 내성과 관련된 유전자에 대해 ShortBRED 마커 (Kaminski et al., 상기)를 사용하여 유전자 존재비를 평가하였다 (Liu and Pop, 2009, ARDB—Antibiotic Resistance Genes Database. Nuc Acids Res 37(Database issue):D443-447). 유의한 수의 종이 투여된 ROAR 조성물에서 확인된 종과 상당히 유전적으로 유사한 것으로 확인된 대상으로 정의된, 유의한 생착 신호에 대해 데이터를 분석하였다. 데이터의 분석 결과, 조성물에 대한 중요한 생착 신호를 갖는 대상체에서, 여러 종류의 약물, 즉, 퀴놀론 약물 (도 1) 및 베타-락탐 또는 카바페넴 약물 (도 2)에 대한 내성과 관련된 유전자의 존재비가 감소함을 발견하였다.

[0131] 추가 분석에서, 각 대상체 및 약물 종류 (1b 상 및 2 상 연구 모두)에 대해, 위약 또는 포자 처리 전날 수집된 샘플과 비교하여, 위약 또는 포자를 투여받은 후 방문 1주에 수집된 샘플 사이의 약물 종류 마커 존재비 (DCMA)의 로그2 배 변화 (로그2FC)를 계산하였다. 위약을 투여받은 rCDI 대상체를 포자를 받고 유의한 생착이 검출된 rCDI 대상체와 비교하였다. 위약을 받은 대상과 비교하여 DCMA의 로그2FC가 포자를 생착한 대상체에서 유의하게 더 큰지를 결정하기 위해 비모수적 맨-휘트니 검사를 사용하였다 (표 2). 여러 검사 실행으로 인한 주어진 p-값에 대해 부정확하게 기각된 귀무 가설의 예상 비율인, 거짓 발견율 (FDR)은 베냐미 호흐베르크 절차를 사용하여 계산하였다 ($p < 0.1$)

[0132] 데이터는 ROAR 조성물이 대상체에서 항생제 내성 유전자의 존재비를 감소시키기 위해 사용될 수 있음을 입증한

다.

표 1 – 처리에 따른 유전자 존재비의 변화

CARD 등록	p-값	FDR	로그 2 생착자 - 로그 2 위약	유전자 기호
ARO_3000753	1.5E-03	8.5E-02	0.91	abeM
ARO_3000216	2.9E-03	8.5E-02	-1.24	acrB
ARO_3000828	2.5E-03	8.5E-02	-1.38	baeR
ARO_3000830	1.3E-03	8.5E-02	-1.57	cpxA
ARO_3002867	2.7E-03	8.5E-02	1.35	dfrF
ARO_3004039	3.7E-03	8.5E-02	-1.27	대장균 emrE
ARO_3002522	2.4E-04	8.5E-02	0.90	novA
ARO_3000196	1.1E-03	8.5E-02	1.72	tet32
ARO_3002871	2.2E-03	8.5E-02	1.46	tet37
ARO_3000195	7.4E-04	8.5E-02	-1.28	tetB(P)
ARO_3002829	3.0E-03	8.5E-02	0.70	vgaA
ARO_3000499	5.1E-03	9.5E-02	-1.47	acrE
ARO_3002626	6.1E-03	9.5E-02	-0.76	ANT(6)-Ia
ARO_3003838	5.7E-03	9.5E-02	-1.50	gadW
ARO_3002836	5.6E-03	9.5E-02	-0.50	lnuB
ARO_3000263	6.7E-03	9.5E-02	-1.33	marA
ARO_3000793	6.3E-03	9.5E-02	-1.40	mdtB
ARO_3000794	6.7E-03	9.5E-02	-1.59	mdtC
ARO_3000180	4.9E-03	9.5E-02	-0.53	tetA(P)
ARO_3000194	5.1E-03	9.5E-02	1.57	tetW
ARO_3003202	5.4E-03	9.5E-02	-0.30	TLA-1
ARO_3000796	7.4E-03	1.0E-01	-1.65	mdtF
ARO_3000615	8.5E-03	1.1E-01	-1.41	mefA
ARO_3002818	8.3E-03	1.1E-01	-1.24	msrB
ARO_3000024	9.0E-03	1.1E-01	-1.02	patA
ARO_3000829	1.0E-02	1.2E-01	-1.47	baeS
ARO_3000491	1.1E-02	1.2E-01	-1.11	acrD
ARO_3000656	1.3E-02	1.2E-01	-1.17	acrS
ARO_3000074	1.1E-02	1.2E-01	-1.10	emrB
ARO_3000309	1.2E-02	1.2E-01	-1.33	emrD
ARO_3000206	1.5E-02	1.2E-01	-1.15	emrK
ARO_3000254	1.4E-02	1.2E-01	-1.42	emrY
ARO_3000833	1.3E-02	1.2E-01	-1.20	evgS
ARO_3000795	1.3E-02	1.2E-01	-1.31	mdtE
ARO_3003550	1.4E-02	1.2E-01	-1.20	mdtP
ARO_3003950	1.3E-02	1.2E-01	-1.48	msbA
ARO_3003952	1.4E-02	1.2E-01	-1.12	yojI

[0133]

ARO_3003549	1.5E-02	1.3E-01	-1.14	mdtO
ARO_3002630	1.8E-02	1.3E-01	-0.41	ANT(9)-Ia
ARO_3002634	1.9E-02	1.3E-01	-1.04	APH(2'')-Ie
ARO_3001328	1.9E-02	1.3E-01	-1.02	대장균 mdfA
ARO_3000832	1.8E-02	1.3E-01	-1.18	evgA
ARO_3000676	1.7E-02	1.3E-01	-1.08	H-NS
ARO_3003206	1.8E-02	1.3E-01	-0.40	lsaE
ARO_3001329	2.0E-02	1.3E-01	-1.05	mdtG
ARO_3001216	1.8E-02	1.3E-01	-1.12	mdtH
ARO_3003107	1.8E-02	1.3E-01	-0.20	mefB
ARO_3002174	2.0E-02	1.3E-01	-1.21	MIR-9
ARO_3000237	1.9E-02	1.3E-01	-1.11	tolC
ARO_3000502	2.4E-02	1.4E-01	-0.91	acrF
ARO_3002986	2.4E-02	1.4E-01	-1.33	bacA
ARO_3002669	2.9E-02	1.5E-01	-0.90	APH(2'')-Ig
ARO_3002152	2.9E-02	1.5E-01	-1.25	DHA-21
ARO_3000516	2.9E-02	1.5E-01	-1.23	emrR
ARO_3002985	3.2E-02	1.7E-01	-0.84	arnA
ARO_3003057	3.4E-02	1.7E-01	-0.23	smeF
ARO_3000803	3.4E-02	1.7E-01	-0.18	MexE
ARO_3001304	3.5E-02	1.7E-01	-0.49	ErmS
ARO_3002559	3.6E-02	1.7E-01	-1.06	AAC(6')-Ip
ARO_3003017	3.7E-02	1.7E-01	-0.09	dfrA21
ARO_3002804	3.7E-02	1.7E-01	-0.37	FosA2
ARO_3002894	3.7E-02	1.7E-01	-0.06	otrC
ARO_3003576	3.7E-02	1.7E-01	-0.89	PmrC
ARO_3003841	3.8E-02	1.7E-01	-0.84	kdpE
ARO_3003578	4.0E-02	1.8E-01	-0.87	pmrF
ARO_3002597	4.4E-02	2.0E-01	-0.93	AAC(6')-Ie-APH(2'')-Ia
ARO_3002635	4.4E-02	2.0E-01	-1.22	APH(2'')-IIa
ARO_3000205	4.8E-02	2.1E-01	-1.14	tetX
ARO_3000192	4.9E-02	2.1E-01	-0.15	tetS
ARO_3004042	5.0E-02	2.1E-01	-1.14	엔테로박터 클로아카 acrA
ARO_3003773	5.6E-02	2.3E-01	-0.04	웰치균 mprF
ARO_3002859	5.6E-02	2.3E-01	0.23	dfrA14
ARO_3003548	5.5E-02	2.3E-01	-0.87	mdtN
ARO_3002688	5.8E-02	2.3E-01	0.21	catS
ARO_3002835	5.8E-02	2.3E-01	-0.21	lnuA
ARO_3000518	6.1E-02	2.3E-01	-0.99	CRP

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ARO_3000792	6.2E-02	2.3E-01	-0.60	mdtA
ARO_3000826	6.1E-02	2.3E-01	-0.90	sdiA
ARO_3002671	6.3E-02	2.3E-01	-0.32	cat-TC
ARO_3003112	6.3E-02	2.3E-01	0.11	lsaC
ARO_3002670	6.9E-02	2.5E-01	0.70	cat
ARO_3000508	6.9E-02	2.5E-01	-0.81	gadX
ARO_3000300	7.0E-02	2.5E-01	-0.22	lsaA
ARO_3003699	7.0E-02	2.5E-01	-0.25	mexQ
ARO_3000191	6.8E-02	2.5E-01	-1.21	tetQ
ARO_3000027	7.2E-02	2.5E-01	-0.76	emrA
ARO_3000377	7.5E-02	2.6E-01	-0.25	MexA
ARO_3003704	8.0E-02	2.6E-01	-0.10	mexM
ARO_3003705	8.0E-02	2.6E-01	-0.24	mexN
ARO_3001421	7.8E-02	2.6E-01	0.03	OXA-26
ARO_3002639	8.3E-02	2.6E-01	-0.51	APH(3'')-Ib
ARO_3004072	8.5E-02	2.6E-01	-0.22	OpmB
ARO_3003681	8.5E-02	2.6E-01	-0.22	TriC
ARO_3002932	8.3E-02	2.6E-01	-0.30	vanSB
ARO_3002831	8.4E-02	2.6E-01	-1.15	vgaC
ARO_3000250	8.9E-02	2.7E-01	-0.27	ErmC
ARO_3002964	8.9E-02	2.7E-01	-0.35	vanWB
ARO_3003679	9.0E-02	2.7E-01	-0.13	TriA
ARO_3002950	9.5E-02	2.8E-01	-0.39	vanXB
ARO_3002553	9.8E-02	2.9E-01	-0.02	AAC(6')-If
ARO_3001777	9.8E-02	2.9E-01	-0.04	OXA-347
ARO_3001303	1.1E-01	3.0E-01	0.07	ErmO
ARO_3000823	1.1E-01	3.0E-01	-0.98	ramA
ARO_3002933	1.1E-01	3.0E-01	-0.12	vanSC
ARO_3003031	1.1E-01	3.1E-01	-0.34	mexW
ARO_3002679	1.1E-01	3.1E-01	-0.25	catB7
ARO_3000578	1.2E-01	3.4E-01	-0.21	CcrA 베타-락타마제
ARO_3002156	1.2E-01	3.4E-01	0.16	FOX-2
ARO_3000811	1.2E-01	3.4E-01	-0.04	mtrD
ARO_3001299	1.2E-01	3.4E-01	0.02	틸로신 내성 부여 tlrB
ARO_3002502	1.3E-01	3.4E-01	-0.23	PDC-5
ARO_3000149	1.3E-01	3.5E-01	-0.15	fosA
ARO_3000378	1.4E-01	3.6E-01	-0.29	MexB
ARO_3002923	1.4E-01	3.6E-01	-0.59	vanRD
ARO_3003577	1.4E-01	3.7E-01	-0.65	pmrE
ARO_3003922	1.4E-01	3.7E-01	-0.99	oqxA

ARO_3000806	1.5E-01	3.7E-01	-0.18	mexG
ARO_3002629	1.5E-01	3.9E-01	0.74	ANT(6)-Ib
ARO_3002868	1.6E-01	3.9E-01	-0.25	dfrG
ARO_3000379	1.6E-01	3.9E-01	-0.14	OprM
ARO_3002687	1.7E-01	4.0E-01	-0.05	catQ
ARO_3002858	1.7E-01	4.0E-01	-0.03	dfrA12
ARO_3000347	1.7E-01	4.0E-01	-0.28	ErmA
ARO_3000807	1.6E-01	4.0E-01	-0.26	mexH
ARO_3000621	1.6E-01	4.0E-01	0.01	PC1 베타-락타마제 (blaZ)
ARO_3003046	1.7E-01	4.0E-01	-0.03	qacA
ARO_3002965	1.6E-01	4.0E-01	-0.26	vanWG
ARO_3002943	1.7E-01	4.0E-01	0.30	vanHB
ARO_3000025	1.7E-01	4.0E-01	0.12	patB
ARO_3004073	1.7E-01	4.0E-01	-0.20	MuxA
ARO_3000368	1.8E-01	4.0E-01	-0.13	vanC
ARO_3002970	1.8E-01	4.1E-01	-0.11	vanTC
ARO_3003698	1.8E-01	4.1E-01	-0.21	mexP
ARO_3003835	1.9E-01	4.2E-01	-0.24	cdeA
ARO_3004077	1.9E-01	4.2E-01	-0.20	PmpM
ARO_3003551	1.9E-01	4.3E-01	-0.19	emeA
ARO_3002528	2.0E-01	4.3E-01	0.02	AAC(3)-Ia
ARO_3002578	2.0E-01	4.3E-01	-0.24	AAC(6')-Ib7
ARO_3002686	2.0E-01	4.3E-01	0.15	catP
ARO_3003693	2.0E-01	4.3E-01	-0.19	mexK
ARO_3002452	2.0E-01	4.3E-01	-0.79	OKP-B-19
ARO_3002957	2.0E-01	4.3E-01	-0.14	vanYD
ARO_3002921	2.0E-01	4.4E-01	-0.38	vanRB
ARO_3001338	2.1E-01	4.4E-01	-0.57	SHV-100
ARO_3004056	2.2E-01	4.5E-01	-0.10	ArmR
ARO_3002317	2.2E-01	4.5E-01	0.00	KPC-7
ARO_3002391	2.1E-01	4.5E-01	-0.94	OXY-1-3
ARO_3000567	2.1E-01	4.5E-01	0.97	tet(40)
ARO_3002185	2.2E-01	4.5E-01	-0.06	MOX-6
ARO_3002972	2.2E-01	4.5E-01	-0.11	vanTG
ARO_3001796	2.3E-01	4.6E-01	-0.23	OXA-50
ARO_3002956	2.3E-01	4.6E-01	-0.40	vanYB
ARO_3002999	2.3E-01	4.7E-01	0.10	CblA-1
ARO_3004036	2.3E-01	4.7E-01	0.02	tetB(60)
ARO_3000316	2.5E-01	5.0E-01	0.05	mphA
ARO_3003923	2.5E-01	5.0E-01	-0.89	oqxB

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ARO_3002930	2.5E-01	5.0E-01	0.19	vanRO
ARO_3003022	2.9E-01	5.1E-01	0.01	dfrB3
ARO_3002705	2.9E-01	5.1E-01	-0.01	floR
ARO_3002213	2.9E-01	5.1E-01	-0.01	IMP-22
ARO_3004041	2.9E-01	5.1E-01	-0.48	폐렴간균 acrA
ARO_3002482	2.9E-01	5.1E-01	-0.05	LRA-1
ARO_3002486	2.9E-01	5.1E-01	0.01	LRA-7
ARO_3001214	2.6E-01	5.1E-01	-0.56	mdtM
ARO_3000215	2.9E-01	5.1E-01	0.00	mecR1
ARO_3001610	2.9E-01	5.1E-01	0.01	OXA-243
ARO_3001503	2.9E-01	5.1E-01	0.03	OXA-258
ARO_3001780	2.7E-01	5.1E-01	0.08	OXA-85
ARO_3003836	2.9E-01	5.1E-01	0.01	qacH
ARO_3002828	2.7E-01	5.1E-01	-0.19	srmB
ARO_3000573	2.9E-01	5.1E-01	0.02	tet(43)
ARO_3000013	2.6E-01	5.1E-01	-0.26	vanB
ARO_3003727	2.9E-01	5.1E-01	0.00	vanKI
ARO_3003724	2.9E-01	5.1E-01	-0.01	vanWI
ARO_3002841	2.9E-01	5.1E-01	0.01	vatB
ARO_3004032	3.0E-01	5.2E-01	0.40	tetA(46)
ARO_3003033	3.1E-01	5.4E-01	-0.20	mexY
ARO_3004033	3.1E-01	5.4E-01	0.36	tetB(46)
ARO_3003209	3.2E-01	5.5E-01	-0.60	FosA5
ARO_3002538	3.8E-01	5.5E-01	0.01	AAC(3)-IIIc
ARO_3002540	3.8E-01	5.5E-01	0.00	AAC(3)-VIa
ARO_3002589	3.8E-01	5.5E-01	0.04	AAC(6')-Iid
ARO_3001816	3.4E-01	5.5E-01	-0.24	ACC-2
ARO_3003848	3.8E-01	5.5E-01	-0.02	ADC-2
ARO_3000780	3.8E-01	5.5E-01	0.02	adeI
ARO_3002646	3.8E-01	5.5E-01	0.01	APH(3')-IIc
ARO_3002660	3.8E-01	5.5E-01	-0.44	APH(6)-Id
ARO_3000838	3.8E-01	5.5E-01	-0.03	arlR
ARO_3000839	3.8E-01	5.5E-01	-0.02	arlS
ARO_3002847	3.8E-01	5.5E-01	-0.04	arr-2
ARO_3002854	3.2E-01	5.5E-01	-0.18	dfrA1
ARO_3003013	3.8E-01	5.5E-01	-0.03	dfrA15
ARO_3002860	3.4E-01	5.5E-01	0.14	dfrA17
ARO_3003953	3.8E-01	5.5E-01	0.01	hmrM
ARO_3002259	3.8E-01	5.5E-01	-0.02	IND-3
ARO_3003111	3.8E-01	5.5E-01	-0.15	lsaB
ARO_3000800	3.2E-01	5.5E-01	-0.17	MexC

ARO_3000808	3.5E-01	5.5E-01	-0.14	mexI
ARO_3003692	3.3E-01	5.5E-01	-0.16	mexJ
ARO_3003035	3.8E-01	5.5E-01	-0.01	mfpA
ARO_3004074	3.3E-01	5.5E-01	-0.08	MuxB
ARO_3000802	3.8E-01	5.5E-01	-0.12	OprJ
ARO_3000805	3.8E-01	5.5E-01	-0.09	OprN
ARO_3001710	3.4E-01	5.5E-01	0.18	OXA-211
ARO_3001398	3.8E-01	5.5E-01	0.02	OXA-3
ARO_3000822	3.6E-01	5.5E-01	0.03	pmrA
ARO_3002794	3.2E-01	5.5E-01	0.01	QnrS5
ARO_3001301	3.5E-01	5.5E-01	0.05	RlmA(II)
ARO_3003056	3.8E-01	5.5E-01	-0.01	smeE
ARO_3002493	3.8E-01	5.5E-01	-0.01	SRT-1
ARO_3000168	3.7E-01	5.5E-01	-0.04	tet(D)
ARO_3000178	3.8E-01	5.5E-01	0.01	tet(K)
ARO_3000186	3.4E-01	5.5E-01	-0.22	tetM
ARO_3000193	3.8E-01	5.5E-01	0.00	tetT
ARO_3000005	3.4E-01	5.5E-01	-0.20	vanD
ARO_3002934	3.6E-01	5.5E-01	-0.47	vanSD
ARO_3002935	3.8E-01	5.5E-01	-0.03	vanSE
ARO_3002953	3.8E-01	5.5E-01	-0.01	vanXM
ARO_3004075	3.8E-01	5.5E-01	-0.15	MuxC
ARO_3000410	3.9E-01	5.6E-01	0.20	sul1
ARO_3002598	4.0E-01	5.7E-01	-0.17	ANT(3'')-Ii-AAC(6')-IId 융합 단백질
ARO_3001396	4.1E-01	5.8E-01	-0.32	OXA-1
ARO_3000616	4.2E-01	5.9E-01	0.12	mel
ARO_3004038	4.3E-01	6.0E-01	-0.20	녹농균 emrE
ARO_3000498	4.4E-01	6.1E-01	-1.33	ErmF
ARO_3004054	4.4E-01	6.2E-01	-0.11	녹농균 CpxR
ARO_3002982	4.6E-01	6.4E-01	-0.11	amrA
ARO_3000593	4.6E-01	6.4E-01	0.19	ErmQ
ARO_3000801	4.6E-01	6.4E-01	-0.18	MexD
ARO_3003839	4.7E-01	6.4E-01	0.11	Mrx
ARO_3003680	4.8E-01	6.6E-01	-0.25	TriB
ARO_3003030	5.2E-01	7.0E-01	-0.17	mexV
ARO_3000167	5.3E-01	7.1E-01	0.02	tet(C)
ARO_3001307	5.3E-01	7.1E-01	-0.02	VgbA
ARO_3003954	5.4E-01	7.2E-01	0.00	efmA
ARO_3000804	5.4E-01	7.2E-01	0.04	MexF
ARO_3000412	5.5E-01	7.3E-01	-0.25	sul2

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ARO_3003583	5.5E-01	7.3E-01	-0.19	basS
ARO_3002684	5.6E-01	7.3E-01	-0.03	catII
ARO_3003948	5.5E-01	7.3E-01	-0.04	efrA
ARO_3000230	5.6E-01	7.3E-01	0.00	ANT(2")-Ia
ARO_3002966	5.8E-01	7.5E-01	-0.15	vanXYC
ARO_3000190	5.8E-01	7.5E-01	0.35	tetO
ARO_3002645	5.9E-01	7.5E-01	-0.11	APH(3')-IIb
ARO_3003097	5.9E-01	7.5E-01	-0.12	CfxA6
ARO_3000522	5.9E-01	7.5E-01	-0.53	ErmG
ARO_3000595	5.9E-01	7.5E-01	-0.30	ErmT
ARO_3002881	6.0E-01	7.5E-01	0.03	ImrC
ARO_3002895	6.0E-01	7.5E-01	-0.16	SAT-1
ARO_3003070	6.0E-01	7.5E-01	-0.13	vanXD
ARO_3002535	6.1E-01	7.5E-01	-0.22	AAC(3)-IIc
ARO_3002539	6.1E-01	7.5E-01	-0.29	AAC(3)-IV
ARO_3000174	6.1E-01	7.5E-01	0.01	tet(G)
ARO_3002944	6.1E-01	7.6E-01	-0.03	vanHD
ARO_3003717	6.4E-01	7.8E-01	-0.05	ESP-1
ARO_3000181	6.4E-01	7.8E-01	0.01	tet(V)
ARO_3003710	6.5E-01	7.9E-01	-0.06	mexL
ARO_3000165	6.5E-01	7.9E-01	-0.15	tet(A)
ARO_3002931	6.5E-01	7.9E-01	-0.03	vanSA
ARO_3000010	6.7E-01	8.1E-01	-0.03	vanA
ARO_3002605	6.7E-01	8.1E-01	0.00	aadA5
ARO_3001933	7.1E-01	8.5E-01	-0.63	CTX-M-72
ARO_3000175	7.1E-01	8.5E-01	0.01	tet(H)
ARO_3002556	7.1E-01	8.5E-01	0.05	AAC(6')-Ii
ARO_3002680	7.2E-01	8.6E-01	-0.25	catB8
ARO_3000809	7.3E-01	8.6E-01	-0.14	opmD
ARO_3002897	7.3E-01	8.6E-01	-0.37	SAT-4
ARO_3001313	7.3E-01	8.6E-01	0.00	facT
ARO_3003197	7.4E-01	8.7E-01	-0.06	aadA25
ARO_3003949	7.7E-01	9.0E-01	0.00	efrB
ARO_3003682	7.7E-01	9.0E-01	-0.13	OpmH
ARO_3001959	7.8E-01	9.0E-01	-0.45	CTX-M-100
ARO_3002942	7.9E-01	9.1E-01	-0.02	vanHA
ARO_3003559	8.1E-01	9.3E-01	-0.29	cepA 베타-락타마제
ARO_3002628	8.2E-01	9.4E-01	-0.02	aad(6)
ARO_3000596	8.2E-01	9.4E-01	0.02	ErmX
ARO_3002949	8.2E-01	9.4E-01	-0.05	vanXA
ARO_3002837	8.3E-01	9.4E-01	-0.30	lnuC

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ARO_3002756	8.3E-01	9.4E-01	0.21	QnrB41
ARO_3002875	8.4E-01	9.4E-01	0.04	dfrE
ARO_3002647	8.5E-01	9.5E-01	0.00	APH(3')-IIIa
ARO_3000179	8.5E-01	9.5E-01	-0.21	tet(L)
ARO_3002069	8.6E-01	9.6E-01	-0.09	CMY-59
ARO_3002019	9.0E-01	9.8E-01	0.01	CMY-8
ARO_3003095	9.0E-01	9.8E-01	0.12	imiS
ARO_3002225	9.0E-01	9.8E-01	-0.03	IMP-34
ARO_3001413	9.0E-01	9.8E-01	0.01	OXA-18
ARO_3000565	9.0E-01	9.8E-01	0.00	tet(38)
ARO_3000177	8.8E-01	9.8E-01	-0.25	tet(J)
ARO_3002882	9.1E-01	9.8E-01	0.07	lmrD
ARO_3002363	9.1E-01	9.8E-01	0.02	PER-1
ARO_3003069	9.1E-01	9.8E-01	-0.02	vanXYG
ARO_3002819	9.2E-01	9.9E-01	-0.03	msrC
ARO_3003210	9.4E-01	9.9E-01	-0.27	FosA4
ARO_3000026	9.4E-01	9.9E-01	-0.01	mepA
ARO_3000746	9.4E-01	9.9E-01	0.00	mepR
ARO_3000815	9.4E-01	9.9E-01	0.00	mgrA
ARO_3003199	1.0E+00	1.0E+00	0.02	AAC(6')-Iak
ARO_3002613	9.6E-01	1.0E+00	0.01	aadA13
ARO_3002641	9.7E-01	1.0E+00	-0.07	APH(3')-Ia
ARO_3002655	1.0E+00	1.0E+00	-0.24	APH(4)-Ia
ARO_3003730	1.0E+00	1.0E+00	-0.06	뮤피로신 내성 부여 비피도박테리아 고유 ileS
ARO_3001920	9.8E-01	1.0E+00	-0.09	CTX-M-59
ARO_3003955	9.9E-01	1.0E+00	-0.03	efpA
ARO_3000375	9.6E-01	1.0E+00	0.07	ErmB
ARO_3004085	1.0E+00	1.0E+00	-0.06	lnuG
ARO_3002665	9.9E-01	1.0E+00	-0.16	npmA
ARO_3003700	9.9E-01	1.0E+00	-0.18	opmE
ARO_3002788	1.0E+00	1.0E+00	-0.04	QnrD1
ARO_3001388	9.6E-01	1.0E+00	-0.37	TEM-211
ARO_3000556	9.5E-01	1.0E+00	-0.01	tet44
ARO_3004035	9.7E-01	1.0E+00	-0.01	tetA(60)
ARO_3002909	1.0E+00	1.0E+00	0.00	vanG
ARO_3002919	9.9E-01	1.0E+00	-0.08	vanRA
ARO_3002922	1.0E+00	1.0E+00	-0.06	vanRC
ARO_3002955	9.5E-01	1.0E+00	0.01	vanYA
ARO_3002962	1.0E+00	1.0E+00	-0.09	vanZA

[0140]

표 2- 포자의 생착은 항생제 내성 유전자의 현저한 감소와 관련이 있음

약물 종류	로그2FC 고 생착자 - 로그2 위약	p-값	FDR	약물 종류 중 항생제의 예시
아미노쿠마린 항생제	-1.634	0.003	0.036	노보비오신, 알바마이신, 루베마이신, 클로로비오신
아미노글리코시드 항생제	-1.241	0.009	0.036	카나마이신, 아미카신, 토브라마이신, 디베카신, 젠타마이신, 시소마이신, 네틸마이신, 네오마이신 (B, C, E) 스트렙토마이신
세팔로스포린	-1.428	0.014	0.036	세파세트릴, 세프라드린, 세프로사딘, 세팔로글리신, 세파클로르, 세팔렉신, 세파드록실, 세파트리진, 세파제돈, 세파피린, 세프메졸, 세파클린, 세파자플루, 세파로틴, 세팔로리딘, 세팔로늄
세파마이신	-1.214	0.008	0.036	세폭시틴, 세포테탄, 세프메타졸
플루오로퀴놀론 항생제	-1.401	0.007	0.036	플루메퀸, 옥솔리닌산, 로속사신, 시프로플록사신, 플레록사신, 로메플록사신, 나디플록사신, 노르플록사신, 오플록사신, 페플록사신, 루플록사신, 발로플록사신, 그레파플록사신, 베보플록사신, 파주플록사신, 스파플록사신, 테마플록사신, 클린나플록사신, 가티플록사신, 목시플록사신, 시타플록사신, 프플리플록사신, 베시플록사신, 엘라플록사신, 오게녹사신, 다노플록사신, 디플록사신, 엔로플록사신, 이바플록사신, 마르보플록사신, 오르비플록사신, 사라플록사신
글리실사이클린	-1.668	0.009	0.036	타이거사이클린
마크로라이드 항생제	-1.288	0.002	0.036	에리스로마이신, 클라리트로마이신, 록시트로마이신
니트로이미다졸 항생제	-1.477	0.013	0.036	니트로이미다졸

[0141]

뉴클레오시드 항생제	-1.347	0.011	0.036	퓨니카마이신, 스트렙토리신
페남	-1.424	0.010	0.036	벤질페니실린
펩티드 항생제	-1.279	0.006	0.036	
페니콜 항생제	-1.139	0.012	0.036	클로람페니콜
리파마이신 항생제	-1.470	0.006	0.036	리파마이신
염화 벤즈알코늄	-1.016	0.019	0.036	염화 벤즈알코늄
모노박탐	-1.114	0.018	0.036	아즈트레오남
페넴	-1.156	0.015	0.036	파로페넴
로다민	-1.016	0.019	0.036	로다민
트리클로산	-1.234	0.018	0.036	트리클로산 항생제
린코사마이드 항생제	-1.123	0.021	0.037	린코마이신, 클린다마이신,피릴리마이신
스트랩토그라민 항생제	-1.065	0.035	0.057	스트렙토그라민
아크리딘 염료	-0.906	0.043	0.067	
카바페넴	-1.239	0.052	0.076	카바페넴
테트라사이클린 항생제	-0.668	0.050	0.076	테트라사이클린
포스포마이신	-1.024	0.066	0.091	포스포마이신

[0142]

[0143] 실시예 2: Abx 내성 유전자의 존재비 변화와 관련된 세균

[0144] 특정 세균 종의 존재가 항생제 내성 유전자의 존재비 감소를 예측하는지를 결정하기 위한 전산 분석을 수행하였다. 이들 분석에서 확인된 종은 설계된 Abx 조성물에 사용될 수 있다. 항균 내성 유전자의 감소와 관련된 미생물 종을 확인하기 위해, 본 발명자들은 종 존재비와 위약에 비해 포자의 생착이 관찰된 대상체에서 유의한 감소를 보인 약물 종류의 DCMA 사이의 스피어맨 상관관계를 계산하였다. P-값은 상기 기재된 바와 같이 베냐미 호흐베르크 절차 ($p < 0.1$)를 사용한 다중 가설 검정을 설명하도록 조정하였다. 항생제 내성 유전자의 적어도 하나의 약물의 현저한 감소와 관련된 종의 세트는 표 3에 요약되어 있다. 본 발명자들은 표 4에 요약된, 적어

도 하나의 종류의 항생제 내성 유전자의 증가된 존재비와 양으로 상관되는 종 세트를 추가로 정의하였다. 모든 표에서 투약량 종은 대상체에게 투여된 투약량 로트에서 확인된 세균 종이다. 본원에 기재된 종의 전장 16S 서열은 표 5 (음의 상관관계) 및 6 (양의 상관관계)에 제공된다. 일부 양태에서, 세균(들)은 아래 열거된 속으로부터 유래된다. 당업자는 표준 방법을 사용하여 속을 식별할 수 있다.

표 3-1 공 이상의 항생제 내성 유전자의 감소와 유의한 상관 관계가 있는 공

종	유의한 감소를 갖는 약물 종류의 수	포자-형성자 (Y/N)	투약량 종(Y/N)	예시 서열 식별자	대표 게놈 수탁 번호(들) (NCBI)
아나에로푸스티스_스테르코리호미니스	21	Y	Y	96, 97	GCF_000154825
아나에로스티페스_카카에	20	Y	N	62-66	GCF_000154305
아나에로스티페스_하드러스	23	Y	Y	223	GCF_000332875
아나에로스티페스_속	24	Y	Y	24	GCA_900066985
아나에로스티페스_미분류	21	N	N		
아나에로트룬쿠스_콜리호미니스	24	Y	Y	89-92	GCF_000154565
아나에로트룬쿠스_미분류	22	N	N		
박테로이데스_프레질리스	18	N	N	184-191	GCF_000273095
박테로이데스_유니포르미스	6	N	N	192-198	GCF_000273275
박테로이데스_벌가투스	16	N	N	199-204	GCF_000273295
블라우티아_페이시스 (a)	22	Y	Y	9	GCA_900066145
블라우티아_페이시스 (b)	24	Y	Y	22	GCA_900066945
블라우티아_히드로게노트로피카	22	Y	Y	101	GCF_000157975
블라우티아_프로덕타	21	Y	Y	281	GCF_000373885
블라우티아_속	22	Y	Y	268, 269	
블라우티아_속_CAG_267	22	Y	Y	261	
블라우티아_벡슬레아	24	Y	Y	104-110, 255	GCF_000159975
클로스트리움과_박테리움_JC118	21	Y	Y	222	GCF_000313565
클로스트리디알레스_박테리움_1_7_47FAA	23	Y	Y	98	GCF_000155435
클로스트리듐_할덴센스	21	Y	Y	278	
클로스트리듐_아스파라기모늄	22	Y	Y	103	GCF_000158075
클로스트리듐_바롤레티	24	Y	Y	80-85	GCF_000154445
클로스트리듐_봄베시	23	Y	Y	73	GCF_000154365
클로스트리듐_클로스트리디오포르메	21	Y	Y	231-233	GCF_000371525
클로스트리듐_하베와이	24	Y	Y	229, 230	GCF_000371445
클로스트리듐_타발렌즈	20	Y	Y	280	
클로스트리듐_셉듐	22	Y	Y	71, 72	GCF_000154345
클로스트리듐_넥실	24	Y	N	282	GCF_000156035
클로스트리듐_라모숨	21	Y	Y	86	GCF_000154485
클로스트리듐_속	21	Y	Y	21	GCA_900066915
클로스트리듐_속	22	Y	Y	18	GCA_900066805
클로스트리듐_속	22	Y	Y	6	GCA_900066055
클로스트리듐_속	22	Y	Y	12	GCA_900066535
클로스트리듐_속	23	Y	Y	11	GCA_900066365
클로스트리듐_속	24	Y	Y	8	GCA_900066135

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클로스트리듐_속	24	Y	Y		
클로스트리듐_속	23	Y	Y	17	GCA_900066795
클로스트리듐_속	22	Y	Y	15, 16	GCA_900066785
클로스트리듐_속	23	Y	Y	10	GCA_900066155
클로스트리듐_신덴스	21	Y	Y	87, 88	GCF_000154505
클로스트리듐_속_CAG_91	23	Y	Y	266	
클로스트리듐_속_KLE_1755	22	Y	N	247	GCF_000466465
클로스트리듐_심비오섬	23	Y	Y	248	GCF_000466485
코프로바실루스_미분류	21	N	N		
코프로코커스_카루스	22	Y	Y	143	GCF_000210555
코프로코커스_코메스	21	Y	Y	99	GCF_000155875
다이얼리스터_인비수스	21	N	N	111-113	GCF_000160055
도레아_포미시게란스	22	Y	Y	114-119	GCF_000169235
도레아_룽키카네	21	Y	Y	60, 61	GCF_000154065
에게르텔라_렌타	22	N	N	39-41	GCF_000024265
에게르텔라_미분류	20	N	N		
이머젠시아_티모넨시스	22	Y	Y	14	GCA_900066695
에리시펠로트리히과_박테리움_21_3	21	N	N	164-168	GCF_000242195
에리시펠로트리히과_박테리움_6_1_45	21	N	N	160-163	GCF_000242175
유박테룸_콘토툼	23	Y	Y	272-275	
유박테룸_엘리겐스	22	Y	Y	43-47	GCF_000146185
유박테룸_하벨레이	22	Y	Y	120	GCF_000173975
유박테룸_라우투스	22	Y	Y	249	GCF_000469345
유박테룸_렉테일	23	Y	Y	34-38	GCF_000020605
유박테룸_속	21	Y	Y		
유박테룸_속_3_1_31	20	Y	Y	205-209, 262	GCF_000273585
유박테룸_벤드리오슘	23	Y	Y	48	GCF_000153885
피칼리박테리움_프로스니지	24	Y	Y	74-79	GCF_000154385
플라보니프랙터_플라우티이	23	Y	Y	158	GCF_000239295
플라보니프랙터_속 (a)	21	Y	Y	19	GCA_900066825
플라보니프랙터_속 (b)	23	Y	Y	13	GCA_900066645
후시카테니박터_사카리보란스	23	Y	Y	4	GCA_001405555
젬미거_포미실리스_(a)	24	Y	Y	256	
젬미거_포미실리스_(b)	24	Y	Y	263	
휴베다니아_펠리포미스	24	Y	Y	102	GCF_000157995
휴베다니아_미분류	24	N	N		
인네스티니모나스_부티리시프로듀센스	23	Y	Y	264	
인네스티니모나스_마실리엔시스	22	N	N	20	GCA_900066895
라효노스피라_젠티노스키자	24	Y	Y	5	GCA_001405835
라효노스피라_젠티노스키자	19	Y	Y	270	

[0146]

[0147]

라효노스피라과_박테리움_1_1_57FAA	23	Y	Y	150	GCF_000218445
라효노스피라과_박테리움_1_4_56FAA	21	Y	Y	145	GCF_000218385
라효노스피라과_박테리움_2_1_58FAA	23	Y	Y	151	GCF_000218465
라효노스피라과_박테리움_3_1_46FAA	22	Y	Y	139	GCF_000209405
라효노스피라과_박테리움_3_1_57FAA_CT1	22	Y	Y	146-148	GCF_000218405
라효노스피라과_박테리움_4_1_37FAA	18	Y	N	137	GCF_000191805
라효노스피라과_박테리움_5_1_57FAA	22	Y	Y	149	GCF_000218425
라효노스피라과_박테리움_5_1_63FAA	24	Y	Y	134	GCF_000185525
라효노스피라과_박테리움_7_1_58FAA	23	Y	Y	159	GCF_000242155
라효노스피라과_박테리움_8_1_57FAA	21	Y	Y	135	GCF_000185545
라효노스피라과_박테리움_9_1_43BFAA	24	Y	Y	141	GCF_000209445
락토니펙터_룸고비토미스	23	Y	Y	271	
오실리발터_미분류	23	N	N		
오실로스피라과_박테리움_VE202_24	23	N	N	265	
파라박테로이데스_미분류	18	N	N		
프레보텔라_부카	22	N	N	133	GCF_000184945
로즈부리아_페이시스	23	Y	Y	259	
로즈부리아_호미니스	21	Y	Y	152-155	GCF_000225345
로즈부리아_인테스티날리스	23	Y	Y	100	GCF_000156535
로즈부리아_이눌리보란스	24	Y	Y	283	GCF_000174195
루마노코쿠스_비셔클란스	23	Y	Y	25, 26	GCA_900067025
루마노코쿠스_브로미	22	Y	Y	142	GCF_000209875
루마노코쿠스_그나부스	23	Y	Y	250-254, 277	GCF_000507805
루마노코쿠스_오베숨_(a)	23	Y	Y	49-53	GCF_000153905
루마노코쿠스_오베숨_(b)	19	Y	Y	267	
루마노코쿠스_속	22	Y	Y	7, 258	GCA_900066095
루마노코쿠스_토크스	24	Y	Y	54-59	GCF_000153925
스트렙토코쿠스_파라산구니스	21	N	N	170-173	GCF_000262145
스트렙토코쿠스_살리바리우스	21	N	N	210-216	GCF_000286295
아들러그라숨속_미분류	23	N	N		
수테렐라_와즈워젠시스	9	N	N	243-246	GCF_000411515
박테로이데스_테타이오타오마이크론	1	N	N	239-242	GCF_000403155
헤모필루스 파라인플루엔자	7	N	N	169	GCF_000261285
파라박테로이데스_디스타소니스	2	N	N	217-221	GCF_000307435
아케르만시아_무치니필라	17	N	N	31-33	GCF_000020225
박테로이데스_도레이	11	N	N	174-183	GCF_000273055
부티비브리오_속	15	N	N	260	
클로스트리듐_시트로니아	20	Y	Y	157	GCF_000233455
클로스트리듐_디피실리	8	Y	N	1-3	GCA_000451045
클로스트리듐_디스포리쿰	9	Y	Y	23	GCA_900066955

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룸로스트리듐_이노큠	4	Y	Y	224-228	GCF_000371425
룸로스트리듐_스피로포메	11	Y	Y	93-95	GCF_000154805
도레아_미분류	13	N	N		
아이젠버그엘라_마설리엔시스	11	Y	Y	257	
아이젠버그엘라_타이_속	14	Y	Y	276	
에리시펠로트리히과_박테리움_2_2_44A	20	N	N	156	GCF_000225685
유박테룸_시래움	14	Y	Y	67-70	GCF_000154325
라뇨노스피라과_박테리움_6_1_63FAA	11	Y	N	140	GCF_000209425
루마노코카과_박테리움_D16	19	Y	Y	121	
루마노코루스_그나부스	7	Y	Y	250-254, 277	GCF_000507805
루마노코루스_속	12	Y	Y	7, 258	GCF_000507805
스트렙토코루스_오스드랄리스	4	N	N	136	GCF_000186465
스트렙토코루스_고르돈디	3	N	N	27-30	GCF_000017005
스트렙토코루스_인굼리스	5	N	N	284-286	GCF_000215385, GCF_000187465, GCF_000223335, GCF_000223255, GCF_000260755
스트렙토코루스_살위니스	5	N	N	138	GCF_000192205
다이소노모나스_모시이	6	N	N	144	GCF_000213575
스트렙토코루스_써모필루스	1	N	N	128-132	GCF_000182875
펩토스스트렙토코카과_노네임_미분류	10	N	N		
루라시발러_미분류	6	N	N		
버크홀더리스속_박테리움_1_1_47	3	N	N	42	GCF_000144975
룸로스트리듐_속_CL_6	4	Y	N	287	
베셀로비브리오_베셀퓨리칸스	1	N	N		GCF_000384815, GCF_000022125, GCF_000420465, GCF_000189295
락토바실러스 퍼멘툼	1	N	N	234-238	GCF_000397165
스트렙토코루스_베스티불라리스	1	N	N	122-127	GCF_000180075

표 4-하나 이상의 종류의 항생제 내성 유전자의 증가된 존재비과 유의하게 양의 상관 관계가 있는 종

종	증가하는 종 존재비와 관련된 약물 종류의 수	포자-형성자 (Y/N)	투약량 종 (Y/N)	예시 서열 식별자	대표 게놈 수탁 번호(들) (NCBI)
캄필로박터_커버스	20	N	N	367	GCF_000376325
시트로박터 프룬디	22	N	N	361, 362	GCF_000312465
시트로박터_미분류	22	N	N		
베실로비브리오_베실류리칸스	6	N	N		GCF_000384815, GCF_000022125, GCF_000420465, GCF_000189295
엔토박터_클로아카에	22	N	N	387	GCF_000467655
엔테로코쿠스_파에칼리스	21	N	N		GCF_000393515, GCF_000394095, GCF_000393615, GCF_000157495, GCF_000390625, GCF_000390925, GCF_000148005, GCF_000148065, GCF_000394075, GCF_000393495, GCF_000391465, GCF_000392675, GCF_000396365, GCF_000157475, GCF_000396665, GCF_000148245, GCF_000393155, GCF_000148165, GCF_000391165, GCF_000157515, GCF_000396085, GCF_000395285, GCF_000479065, GCF_000393095, GCF_000393255, GCF_000391065, GCF_000394955, GCF_000415065, GCF_000394975, GCF_000415085, GCF_000395405, GCF_000172575,

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					GCF_000390525, GCF_000393115, GCF_000394775, GCF_000393475, GCF_000390705, GCF_000205205, GCF_000395135, GCF_000392815, GCF_000320305, GCF_000396205, GCF_000390665, GCF_000390685, GCF_000391725, GCF_000163815, GCF_000391605, GCF_000391445, GCF_000391425, GCF_000396185, GCF_000148445, GCF_000148125, GCF_000396605, GCF_000396045, GCF_000291565, GCF_000394315, GCF_000395035, GCF_000147455, GCF_000391345, GCF_000396525, GCF_000392755
대장균	24	N	N	388-394	GCF_000474825
대장균_미분류	23	N	N		
푸소박테리움_뉴클레아툼	15	N	N	403	GCF_000479185
클렙시엘라_옥시토카	22	N	N	330	GCF_000252915
클렙시엘라_뉴모니아	22	N	N	395-402	GCF_000474865
클렙시엘라_미분류	21	N	N		
락토바실루스_애니말리스	22	N	N	317	GCF_000183825
락토바실루스_카세이_파라카세이	22	N	N	378, 379, 381-385	GCF_000409835, GCF_000418515
락토바실루스_플란타룸	22	N	N	386	GCF_000463075
락토바실루스_달노서스	24	N	N	328, 329	GCF_000235785
락토바실루스_살리바리우스	9	N	N	303	GCF_000159395
락토코쿠스_락티스	15	N	N	363, 364	GCF_000348965
메가스파아에라_마이크로누시포미스	22	N	N	310	GCF_000165735
메가스파아에라_미분류	11	N	N		
모르가넬라_모르가니	24	N	N	355	GCF_000286435
프로테아_미분류	24	N	N		
페디오코쿠스_에시디락티시	19	N	N	299	GCF_000146325

[0151]

프로테우스_펜네리	17	N	N	301, 302	GCF_000155835
스트렙토코쿠스_미티스_오랄리스_뉴모니아	3	N	N	288-291, 332	GCF_000014365, GCF_000257865
스트렙토코쿠스_써모필루스	5	N	N	312-316	GCF_000182875
베일로넬라_아티피카	19	N	N	311	GCF_000179755
베일로넬라_디스파	18	N	N	304-306	GCF_000160015
베일로넬라_파볼라	13	N	N	322	GCF_000215025
비피도박테리움_덴티움	1	N	N	300	GCF_000146775
부티비브리오_속	1	N	N	404	
클로스트리듐_속_CL_6	1	Y	N	287	NCBI Taxonomy ID 1499683
덴트로코커스 페시움	18	N	N	380	GCF_000414965
에리시펠로트리히과_박테리움_2_2_44A	1	N	N	326	GCF_000225685
락토바실러스 퍼멘툼	2	N	N	368-372	GCF_000397165
락토바실러스_가세리	1	N	N	377	GCF_000406345
프로테우스_미라빌리스	8	N	N	292-298	GCF_000069965
로티아_덴트카리오사	5	N	N	307-309	GCF_000164695
프로테우스_미분류	5	N	N		
베일로넬라_미분류	14	N	N		
알리스티페스_온네드덴키이	1	N	N	365, 366	GCF_000374505
박테로이데스_오바투스	5	N	N	333-336	GCF_000273195
박테로이데스_벌가투스	4	N	N	344-349	GCF_000273295
빌로넬라_미분류	3	N	N		
빌로넬라_와즈워시아	3	N	N	318-321	GCF_000185705
파라박테로이데스_디스타소니스	6	N	N	356-360	GCF_000307435
파라박테로이데스_미분류	3	N	N		
알리스티페스_미분류	2	N	N		
로티아_무실라기노사	1	N	N	327	GCF_000231235
박테로이데스_테타이오타오마이크론	1	N	N	373-376	GCF_000403155
박테로이데스_유니포르미스	2	N	N	337-343	GCF_000273275
에게르텔라_미분류	1	N	N		
유박테륨_속_3_1_31	2	Y	Y	350-354	GCF_000273585
라쵸노스피라과_박테리움_3_1_57FAA_CT1	1	Y	Y	323-325	GCF_000218405
루마노코쿠스_오베움	1	Y	Y	405	
투라시발터_미분류	1	N	N		
클로스트리듐_퍼프린젠스	1	Y	Y	331	GCF_000255475

[0152] *표 5 - 종의 전장16S rDNA서열 (음의 상관관계)*

종 명	서열 식별자	16S rDNA 서열
클로스트리듐_디피실리	서열 번호 1	ttatgagagtttgatcctggctcaggacgaacgctggcggcgtgcctaatacatgcaagtcgaacgcttcttttccaccggagcttgctccacc ggaaaaagaggagtggcgaacgggtgagtaacacgtgggtaacctgcccatcagaaggggataacacttggaaacaggtgctaataccgt ataacaatcgaaaccgcatggttttgatttgaaaggcgctttcgggtgtcgctgatggatggacccgcggtgcattagctagttggtgaggtaac ggctcaccaaggccacgatgcatagccgacctgagagggtgatcggccacattgggactgagacacggcccaaactcctacgggaggca gcagtagggaatcttcggcaatggacgaaagtctgaccgagcaacgccgcgtgagtgaagaaggttttcggatcgtaaaactctgttgttaga gaagaacaaggatgagagtaactgttcatcccttgacggtatctaaccagaaagccacggctaactacgtgccagcagccgcggtaatacgt aggtggcaagcgttgtccggatttattgggcgtaaagcgagcgcaggcggtttcttaagtctgatgtgaaagccccgggctcaaccgggggag ggtcattggaaactgggagacttgagtgcagaagaggagagtggaattccatgtgtagcggtgaaatgcgtagatatatggaggaacaccag tggcgaaggcggctctctggtctgtaactgacgctgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgt aaacgatgagtgctaagtgttggagggtttccgcccttca
클로스트리듐_디피실리	서열 번호 2	ttatgagagtttgatcctggctcaggacgaacgctggcggcgtgcctaatacatgcaagtcgaacgcttcttttccaccggagcttgctccacc ggaaaaagaggagtggcgaacgggtgagtaacacgtgggtaacctgcccatcagaaggggataacacttggaaacaggtgctaataccgt ataacaatcgaaaccgcatggttttgatttgaaaggcgctttcgggtgtcgctgatggatggacccgcggtgcattagctagttggtgaggtaac ggctcaccaaggccacgatgcatagccgacctgagagggtgatcggccacattgggactgagacacggcccaaactcctacgggaggca gcagtagggaatcttcggcaatggacgaaagtctgaccgagcaacgccgcgtgagtgaagaaggttttcggatcgtaaaactctgttgttaga gaagaacaaggatgagagtaactgttcatcccttgacggtatctaaccagaaagccacggctaactacgtgccagcagccgcggtaatacgt aggtggcaagcgttgtccggatttattgggcgtaaagcgagcgcaggcggtttcttaagtctgatgtgaaagccccgggctcaaccggggag ggtcattggaaactgggagacttgagtgcagaagaggagagtggaattccatgtgtagcggtgaaatgcgtagatatatggaggaacaccag tggcgaaggcggctctctggtctgtaactgacgctgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgt aaacgatgagtgctaagtgttggagggtttccgcccttca
클로스트리듐_디피실리	서열 번호 3	ttatgagagtttgatcctggctcaggacgaacgctggcggcgtgcctaatacatgcaagtcgaacgcttcttttccaccggagcttgctccacc ggaaaaagaggagtggcgaacgggtgagtaacacgtgggtaacctgcccatcagaaggggataacacttggaaacaggtgctaataccgt ataacaatcgaaaccgcatggttttgatttgaaaggcgctttcgggtgtcgctgatggatggacccgcggtgcattagctagttggtgaggtaac ggctcaccaaggccacgatgcatagccgacctgagagggtgatcggccacattgggactgagacacggcccaaactcctacgggaggca gcagtagggaatcttcggcaatggacgaaagtctgaccgagcaacgccgcgtgagtgaagaaggttttcggatcgtaaaactctgttgttaga gaagaacaaggatgagagtaactgttcatcccttgacggtatctaaccagaaagccacggctaactacgtgccagcagccgcggtaatacgt aggtggcaagcgttgtccggatttattgggcgtaaagcgagcgcaggcggtttcttaagtctgatgtgaaagccccgggctcaaccggggag ggtcattggaaactgggagacttgagtgcagaagaggagagtggaattccatgtgtagcggtgaaatgcgtagatatatggaggaacaccag tggcgaaggcggctctctggtctgtaactgacgctgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgt aaacgatgagtgctaagtgttggagggtttccgcccttca
후시카베니박터_사카리보탄스	서열 번호 4	tcagagagtttgatcctggctcaggatgaacgctggcggcgtgcttaacacatgcaagtcgagcgaagcagttaagttgatttcttcggattgat tcttgactgactgagcggcggacgggtgagtaacgcgtgggtgacctgccccatacccgggggataacagctggaaacggctgctaataccg cataagcgcacagagctgcatggctcggtgtgaaaaactccggtggtatgggatgggcccgcgtctgattaggcagttggcggggtaacgg cccaccaaaccgacgatcagtagccggcctgagagggcgaccggccacattgggactgagacacggcccaaactcctacgggaggcag cagtggggaatattgcacaatgggggaaaccctgatgcagcgacgccgcgtgagcgaagaagtatttcggtatgtaaagctctatcagcagg gaagaataatgacggtacctgactaagaagccccggctaactacgtgccagcagccgcggtaatacgtagggggcaagcgttatccggattta ctgggtgtaaagggagcgtagacggcaaggcaagtctgatgtgaaaacccagggcttaaccctgggactgcattggaaactgtctggctcg agtgccggagaggtaagcggaattcctagtgtagcggtgaaatgcgtagatattaggaagaacaccagtggcgaaggcggcttactggacg gtaactgacgttgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgtaaacgatgaatgctaggtgttggg gagcaaagctcttcggtgccgccgcaaacgcattaagcattccacctggggagtacgttcgcaagaatgaaactcaaaggaattgacgggg acccgcacaagcggtggagcatgtggtttaattcgaagcaacgcgaagaaccttaccaggtcttgacatcccgatgaccggcccgtaacgg ggctttctcttcggagcattggagacaggtggtgcatggttgtcgtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaacc cttatcctcagtagccagcaggtaaagctggcactctgtggagactgccagggataacctggaggaaggtggggatgacgtcaaatcatca tgcccccttatgatctgggctacacacgtgctacaatggcgtaaacaaagggaggcaaagccgcgaggtggagcaaatcccaaaaataacgt ctcagttcggactgcagtctgcaactcgactgcacgaagctggaatcgctagtaatcgcgaatcagaatgtcgcggtgaatacgttcccgggt cttgtacacaccgcccgtcacacatgggagttggtaacgcccgaagtcagtgacccaacctttaggagggagctgccgaaggcgggact gataactggggtgaagtcgtaacaaggtagccgtatcggaaggtgcggctggatcacctcctt
라호노스피라_메티노스치자	서열 번호 5	ttatgagagtttgatcctggctcaggatgaacgctggcggcgtgcttaacacatgcaagtcgaacgaagcatttaagacagattacttcggtttg aagtcttttatgactgagtggcggacgggtgagtaacgcgtgggtaacctgcctcatacaggggatagcagctggaaacggctggtaatac cgcataagcgcacagtaccacatggtacagtgtgaaaaactccggtggtatgagatggacccgcgtctgattagcttgttggcggggtaacg gcccaccaaggcgacgatcagtagccgacctgagagggtgaccggccacattgggactgagacacggcccagactcctacgggaggca gcagtggggaatattgcacaatgggaggaaactctgatgcagcgacgccgcgtgagtgaagaagtagttcgctatgtaaagctctatcagcag ggaagatagtgacggtacctgactaagaagctccggctaaatacgtgccagcagccgcggtaatacgtatggagcaagcgttatccggattt actgggtgtaaagggagtgtaggtggccaggcaagtcagaagtgaaagcccggggctcaaccccgggactgcttttgaaactgcagggct agagtgcaggagggcaagtggaattcctagtgtagcggtgaaatgcgtagatattaggaggaacaccagtggcgaaggcggcttgctgg actgtaactgacactgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgtaaacgatgaatactaggtgtc ggggcacataagtgctccggtgccgcagcaaacgcaataagtattccacctggggagtacgttcgcaagaatgaaactcaaaggaattgac ggggacccgcacaagcggtggagcatgtggtttaattcgaagcaacgcgaagaaccttaccaagtcttgacatcctcttgaccggtcagtaat gtgacctttttcttcggaacaagagtgacaggtggtgcatggttgtcgtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaa ccctttatccttagtagccagcagttcggctggcactctaggggagactgccagggataacctggaggaaggtggggatgacgtcaaatcatc atgcccccttatgacttgggctacacacgtgctacaatggcgtaaacaaagtgaagcgagagcgtgagcttaagcaaatcacaaaaataacgtc

[0153]

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클로스트리듐_속	서열 번호 6	tccggtggtatgagatggacccgcgtctgattagctagttggtgaggtaacggcccaccaaggcgacgatcagtagccgacctgagagggt gaccggccacattgggactgagacacggcccagactcctacgggaggcagcagtgggggatattgcacaatggaggaaactctgatgcag cgacgccgcgtgagtgaagaagtatttcggtatgtaaagctctatcagcagggaagaaaatgacggtacctgactaagaagccccggctaac tacgtgccagcagccgcggtaatacgtaggggcaagcgttatccggatttactgggtgtaaagggagcgtagacggcgacgcaagtctga agtgaaatacccgggctcaacctgggaactgctttggaaactgtgttgctagagtgctggagaggtaagcggaattcctagtgtagcggtgaa atgcgtagatattaggaagaacaccagtggcgaaggcggcttactggacagtaactgacgttgaggctcgaaagcgtggggagcaaacag gattagataccctggtagtccacgccgtaaacgatgaatactaggtgttggtgagcaaagctcatcggtgccgccgcaaacgcaataagtatt ccacctggggagtacgttcgcaagaatgaaactcaaaggaattgacggggacccgcacaagcggtggagcatgtggtttaattcgaagcaa cgcgaagaaccttaccaaatcttgacatcccctctgaaaagcctttaatcgggctcctccttcgggacagaggtgacaggtggtgcatggttgtc gtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaaccccttattgtcagtagccagcaggtaaagctgggcactctgatga gactgccaggataacctggaggaaggtggggatgacgtcaaatcatcatgccccttatgatttgggctacacacgtgctacaatggcgtaaa caaagagaagcgagcctgcgagggggagcaaatctcaaaaataacgtctcagttcggattgtagtctgcaactcgactacatgaagctggaa tcgctagtaatcgcagatcagaatgctgcggtgaatacgttcccgggtcttgtacacaccgcccgtcacaccatgggagtcggaaatgcccga agccagtgacccaagcgaaagcagggagctgtcgaaggcaggtctgataactggggtgaagtcgtaacaaggtagccgtatcggaaggtg cggctggatcacctccttt
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[0183]

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[0204]

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클로스트리듐_라발렌즈	서열 번호 280	tttgagagtttgatcctggctcaggatgaacgctggcggcgtgcttaacacatgcaagtcgaacgaagcatttcagatgaagttttcggatgga ttctgagatgactgagtggcggacgggtgagtaacacgtggataacctgcctcacactgggggacaacagttagaaatgactgctaataccg cataagcgcacagtaccgcatggtacagtgtgaaaaactccggtggtgtgagatggatccgcgtctgattagccagttggcggggtaacggc ccaccaaagcgacgatcagtagccgacctgagagggtgaccggccacattgggactgagacacggcccaaactcctacgggaggcagca gtggggaatattgcacaatgggcgaaagcctgatgcagcgacgccgcgtgagtgaagaagtatttcggtatgtaaagctctatcagcaggga agataatgacggtacctgactaagaagccccggctaactacgtgccagcagccgcggtaatacgtaggggcaagcgttatccggatttact gggtgtaaagggagcgtagacggcatggcaagtctgaagtgaaaacccagggctcaaccctgggactgctttggaaactgtcaagctagag tgcaggagaggtaagtggaattcctagtgtagcggtgaaatgcgtagatattaggaggaacaccagtggcgaaggcggcttactggactgta actgacgttgaggctcgaaagcgtggggagcaaacaggattagataccctggtagtccacgccgtaaacgatgagtgctaggtgttggggg gcaaagcccttcggtgccgtcgcaaacgcaataagcactccacctggggagtacgttcgcaagaatgaaactcaaaggaattgacggggac ccgcacaagcggtggagcatgtggtttaattcgaagcaacgcgaagaaccttaccaagtcttgacatcctcttgaccggcgtgtaacggcgcc tttccttcgggacaagggagacaggtggtgcatggttgtcgtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaacccctta tccttagtagccagcattaagatgggcactctagggagactgccagggacaacctggaggaaggtggggatgacgtcaaatcatcatgccc cttatgatttgggctacacacgtgctacaatggcgtaaacaaagggaagcgacctgcgaaggtgagcaaatctcaaaaataacgtcccagtt cggactgtagtctgcaacccgactacacgaagctggaatcgctagtaatcgcgaatcagaatgtcgcggtgaatacgttcccgggtcttgtac acaccgcccgtcacaccatgggagtcagcaacgcccgaagtcagtgacccaactcgcaagagagggagctgccgaaggcggggcaggt aactggggtgaagtcgtaacaaggtagccgtatcggaaggtgcggctggatcacctcctt
블라우티아_프로덕타	서열 번호 281	AGAGTTTGATCCTGGCTCAGGATGAACGCTGGCGGCGTGCTTAACACATGCAAGTCG AGCGAAGCACTAAGACGGATTTCTTCGGATTGAAGTCTTTGTGACTGAGCGGCGGAC GGGTGAGTAACGCGTGGGTAACCTGCCTCATACAGGGGGATAACAGTTAGAAATGAC TGCTAATACCGCATAAGCGCACAGGACCGCATGGTCTGGTGTGAAAAACTCCGGTGG TATGAGATGGACCCGCGTCTGATTAGCTAGTTGGAGGGGTAACGGCCCACCAAGGCG ACGATCAGTAGCCGGCCTGAGAGGGTGAACGGCCACATTGGGACTGAGACACGGCCC AGACTCCTACGGGAGGCAGCAGTGGGGAATATTGCACAATGGGGGAAACCCTGATGC AGCGACGCCGCGTGAAGGAAGAAGTATCTCGGTATGTAAACTTCTATCAGCAGGGAA GAAAATGACGGTACCTGACTAAGAAGCCCCGGCTAACTACGTGCCAGCAGCCGCGGT AATACGTAGGGGGCAAGCGTTATCCGGATTTACTGGGTGTAAAGGGAGCGTAGACGG AAGAGCAAGTCTGATGTGAAAGGCTGGGGCTTAACCCCAGGACTGCATTGGAAACTG TTGTTCTAGAGTGCCGGAGAGGTAAGCGGAATTCCTAGTGTAGCGGTGAAATGCGTA GATATTAGGAGGAACACCAGTGGCGAAGGCGGCTTACTGGACGGTAACTGACGTTGA GGCTCGAAAGCGTGGGGAGCAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAA CGATGAATACTAGGTGTCGGGTGGCAAAGCCATTCGGTGCCGCAGCAAACGCAATAA GTATTCCACCTGGGGAGTACGTTCGCAAGAATGAAACTCAAAGGAATTGACGGGGAC CCGCACAAGCGGTGGAGCATGTGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAA GTCTTGACATCCCTCTGACCGTCCCGTAACGGGGACTTCCCTTCGGGGCAGAGGAGAC AGGTGGTGCATGGTTGTCGTCAGCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAAC GAGCGCAACCCTTATCCTTAGTAGCCAGCACATGATGGTGGGCACTCTAGGGAGACT GCCGGGGATAACCCGGAGGAAGGCGGGGACGACGTCAAATCATCATGCCCCTTATGA TTTGGGCTACACACGTGCTACAATGGCGTAAACAAAGGGAAGCGAGACAGCGATGTT GAGCGAATCCCAAAAATAACGTCCCAGTTCGGACTGCAGTCTGCAACTCGACTGCAC GAAGCTGGAATCGCTAGTAATCGCGGATCAGAATGCCGCGGTGAATACGTTCCCGGG TCTTGTACACACCGCCCGTCACACCATGGGAGTCAGTAACGCCCGAAGTCAGTGACC TAACCGAAAGGAAGGAGCTGCCGAAGGCGGGACCGATAACTGGGGTGAAGTCGTAA CAAGGTAACC
클로스트리듐_넥실	서열 번호 282	NNNNNNGAGATTTGATCCTGGCTCAGGATGAACGCTGGCCGGCCGTGCTTACACAT GCAGTCGAACGAAGCGCTTAAACTGGATTTCTTCGGATTGAAGTTTTTGCTGACTGAG TGGCGGACGGGTGAGTAACGCGTGGGTAACCTGCCTCATACAGGGGGATAACAGTTA GAAATGACTGCTAATACCNNATAAGCGCACAGTGCTGCATGGCACAGTGTAAAAACT CCGGTGGTATGAGATGGACCCGCGTCTGATTAGCTAGTTGGTGGGGTAACGGCCTAC CAAGGCGACGATCAGTAGCCGGCCTGAGAGGGTGAACGGCCACATTGGGACTGAGA CACGGNCCAAACTCCTACGGGAGGCAGCAGTGGGGAATATTGCACAATGGGGGAAA CCCTGATGCAGCGACGCCGCGTGAGCGAAGAAGTATTTNGGTATGTAAAGCTCTATC AGCAGGGAAGAAAATGACGGTACCTGACTAAGAAGCACCGGCTAAATACGTGCCAG CAGCCGCGGTAATACGTAGGTGCAAGCGTTATCCGGATTTACTGGGTGTAAAGGGAG CGTAGACGGTTGTGTAAGTCTGATGTGAAAGCCCGGGGCTCAACCCCGGACTGCATT GGAAACTATGTAACTAGAGTGTCGGAGAGGTAAGCGGAATTCCTAGTGTAGCGGTGA AATGCGTAGATATTAGGAGGAACACCAGTGGCGAAGGCGGCTTACTGGACGATCACT GACGTTGAGGCTCGAAAGCGTGGGGAGCAAACAGGATTAGATACCCTGGTAGTCCAC GCCGTAAACGATGACTACTAGGTGTCGGGGAGCAAAGCTCTTCGGTGCCGCAGCAAA

[0224]

		CGCAATAAGTAGTCCACCTGGGGAGTACGTTCGCAAGAATGAAACTCAAAGGAATTG ACGGGGACCCGCACAAGCGTGGAGCATGTGGTTTAATTCGAGCAACGCGAAGACCTT ACCTGGTCTTGACATCCCGGTGACCGGTCCAGTAATGGGACCTTTCCTTCGGGACACG GTGACAGGTGGTGCATGGTTGTCGTCAGCTCGTGTCGTGAGATGTTGGGTTAAGTCCC GCAACGAGCGCAACCCCTATCTTCAGTAGCCAGCATTTAAGGTGGGCACTCTGGAGA GACTGCCAGGGATAACCTGGAGGAAGGTGGGGATGACGTCAAATCATCATGCCCCTT ATGACCAGGGCTACACACGTGCTACAATGGCGTAAACAAAGGGAAGCGAACCTGTG AGGGGAAGCAAATCTCAAAAATAACGTCTCAGTTCGGATTGTAGTCTGCAACTCGAC TACATGAAGCTGGAATCGCTAGTAATCGCGAATCAGCATGTCGCGGTGAATACGTTC CCGGGTCTTGTACACACCGCCCGTCACACCATGGGAGTCAGTAACGCCCGAAGTCAG TGACCCAACCGTAAGGAGGGAGCTGCCGAAGGTGGGACCGATAACTGGGGTGAAGT CGTAACAAGGTAGCCGTATCGGAAGGTGCGGCTGGATCACCTCC
로즈부리아_이눌리보란스	서열 번호 283	TTGATCCTGGCTCAGGATGAACGCTGGCGGCGTGCTTAACACATGCAAGTCGAACGA AGCACTTTTACAGATTTCTTCGGAATGAAGTTTTAGTGACTGAGTGGCGGACGGGTGA GTAACGCGTGGGTAACCTGCCTCACACAGGGGGATAACAGTTGGAAACGGCTGCTAA TACCGCATAAGCGCACAGTACCGCATGGTACAGTGTGAAAAACTCCGGTGGTGTGAG ATGGACCCGCGTCTGATTAGCTAGTTGGCAGGGCAACGGCCTACCAAGGCGACGATC AGTAGCCGACCTGAGAGGGTGACCGGCCACATTGGGACTGAGACACGGCCCAAACTC CTACGGGAGGCAGCAGTGGGGAATATTGCACAATGGGGGAAACCCTGATGCAGCGA CGCCGCGTGAGCGAAGAAGTATTTCGGTATGTAAAGCTCTATCAGCAGGGAAGAAGA AATGACGGTACCTGACTAAGAAGCACCGGCTAAATACGTGCCAGCAGCCGCGGTAAT ACGTATGGTGCAAGCGTTATCCGGATTTACTGGGTGTAAAGGGAGCGCAGGCGGAAG GCTAAGTCTGATGTGAAAGCCCGGGGCTCAACCCCGGTACTGCATTGGAAACTGGTC ATCTAGAGTGTCGGAGGGGTAAGTGGAATTCCTAGTGTAGCGGTGAAATGCGTAGAT ATTAGGAGGAACACCAGTGGCGAAGGCGGCTTACTGGACGATAACTGACGCTGAGGC TCGAAAGCGTGGGGAGCAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGA TGAATACTAGGTGTCGGAAAGCACAGCTTTTCGGTGCCGCCGCAAACGCATTAAGTA TTCCACCTGGGGAGTACGTTCGCAAGAATGAAACTCAAAGGAATTGACGGGGACCCG CACAAGCGGTGGAGCATGTGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAAGTC TTGACATCCTTCTGACCGGACAGTAATGTGTCCTTTCCTTCGGGACAGAAGTGACAGG TGGTGCATGGTTGTCGTCAGCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAACGAG CGCAACCCTTATCCCCAGTAGCCAGCGGTTCGGACGGGCACTCTGAGGAGACTGCCA GGGATAACCTGGAGGAAGGTGGGGATGACGTCAAATCATCATGCCCCTTATGACTTG GGCTACACACGTGCTACAATGGCGTAAACAAAGGGAAGCGAGACCGTGAGGTGGAG CAAATCCCAAAAATAACGTCTCAGTTCGGACTGTAGTCTGCAACCCGACTACACGAA GCTGGAATCGCTAGTAATCGCAGATCAGAATGCTGCGGTGAATACGTTCCCGGGTCTT GTACACACCGCCCGTCACACCATGGGAGTTGGAAATGCCCGAAGTCAGTGACCCAAC CGCAAGGAGGGAGCTGCGAAGGCAGGT
스트렙토코루스_인판티스	서열 번호 284	GAACGGGTGAGTAACGCGTAGGTAACCTGCCTGGTAGCGGGGGATAACTATTGGAAA CGATAGCTAATACCGCATAACAGTAGATATCGCATGATAGCTGCTTGAAAGGTGCAA TTGCACCACTACCAGATGGACCTGCGTTGTATTAGCTAGTTGGTGAGGTAACGGCTCA CCAAGGCRACGATACATAGCCGACCTGAGAGGGTGATCGGCCACACTGGGACTGAGA CACGGCCCAGACTCCTACGGGAGGCAGCAGTAGGGAATCTTCGGCAATGGACGGAA GTCTGACCGAGCAACGCCGCGTGAGTGAAGAAGGTTTTCGGATCGTAAAGCTCTGTT GTAAGAGAAGAACGAGTGTGAGAGTGGAAAGTTCACACTGTGACGGTATCTTACCAG AAAGGGACGGCTAACTACGTGCCAGCAGCCGCGGTAATACGTAGGTCCCGAGCGTTG TCCGGATTTATTGGGCGTAAAGCGAGCGCAGGCGGTTAGATAAGTCTGAAGTTAAAG GCTGTGGCTTAACCATAGTACGCTTTGGAAACTGTTTAACTTGAGTGCAAGAGGGGA GAGTGGAATTCCATGTGTAGCGGTGAAATGCGTAGATATATGGAGGAACACCGGTGG CGAAAGCGGCTCTCTGGCTTGTAACTGACGCTGAGGCTCGAAAGCGTGGGGAGCAAA CAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGAGTGCTAGGTGTTAGACC CTTTCCGGGGTTTAGTGCCGAAGCTAACGCATTAAGCACTCCGCCTGGGGAGTACGA CCGCAAGGTTGAAACTCAAAGGAATTGACGGGGGCCCGCACAAGCGGTGGAGCATG TGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAGGTCTTGACATCCCTCTGACCGC TCTAGAGATAGAGTTTTCCTTCGGGACAGAGGTGACAGGTGGTGCATGGTTGTCGTCA GCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCCTATTGTTAGT TGCCATCATTYAGTTGGGCACTCTAGCGAGACTGCCGGTAATAAACCGGAGGAAGGT GGGGATGACGTCAAATCATCATGCCCCTTATGACCTGGGCTACACACGTGCTACAAT GGTTGGTACAACGAGTCGCAAGCCGGTGACGGCAAGCTAATCTCTTAAAGCCAATCT CAGTTCGGATTGTAGGCTGCAACTCGCCTACATGAAGTCGGAATCGCTAGTAATCGC GGATCAGCACGCCGCGGTGAATACGTTCCCGGGCCTTGTACACACCGCCCGTCACAC CACGAGAGTTTGTAAC
스트렙토코루스_인판티스	서열 번호 285	TGCCTAATACATGCAAGTAGAACGCTGAAGGAGGAGCTTGCTCTTCTGGATGAGTTG CGAACGGGTGAGTAACGCGTAGGTAACCTGCCTGGTAGCGGGGGATAACTATTGGAA

[0225]

		ACGATAGCTAATACCGCATAACAGTAGATATCGCATGATAGCTGCTTGAAAGGTGCA ATTGCACCACTACCAGATGGACCTGCGTTGTATTAGCTAGTTGGTGAGGTAACGGCTC ACCAAGGCAACGATACATAGCCGACCTGAGAGGGTGATCGGCCACACTGGGACTGA GACACGGCCCAGACTCCTACGGGAGGCAGCAGTAGGGAATCTTCGGCAATGGACGG AAGTCTGACCGAGCAACGCCGCGTGAGTGAAGAAGGTTTTCGGATCGTAAAGCTCTG TTGTAAGAGAAGAACGAGTGTGAGAGTGGAAAGTTCACACTGTGACGGTATCTTACC AGAAAGGGACGGCTAACTACGTGCCAGCAGCCGCGGTAATACGTAGGTCCCGAGCGT TGTCCGGATTTATTGGGCGTAAAGCGAGCGCAGGCGGTTAGATAAGTCTGAAGTTAA AGGCTGTGGCTTAACCATAGTACGCTTTGGAAACTGTTTAACTTGAGTGCAAGAGGG GAGAGTGGAATTCCATGTGTAGCGGTGAAATGCGTAGATATATGGAGGAACACCGGT GGCGAAAGCGGCTCTCTGGCTTGTAACTGACGNGAGGCTCGAAAGCGTGGGGAGCAA ACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGAGTGCTAGGTGTTAGAC CCTTTCCGGGGTTTAGTGCCGTAGCTAACGCATTAAGCACTCCGCCTGGGGAGTACGA CCGCAAGGTTGAAACTCAAAGGAATTGACGGGGGCCCGCACAAGCGGTGGAGCATG TGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAGGTCTTGACATCCCTCTGACCGC TCTAGAGATAGAGTTTTCCTTCGGGACAGAGGTGACAGGTGGTGCATGGTTGTCGTCA GCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCCTATTGTTAGT TGCCATCATTCAGTTGGGCACTCTAGCGAGACTGCCGGTAATAAACCGGAGGAAGGT GGGGATGACGTCAAATCATCATGCCCCTTATGACCTGGGCTACACACGTGCTACAAT GGTTGGTACAACGAGTCGCAAGCCGGTGACGGCAAGCTAATCTCTTAAAGCCAATCT CAGTTCGGATTGTAGGCTGCAACTCGCCTACATGAAGTCGGAATCGCTAGTAATCGC GGATCAGCACGCCGCGGTGAATACG
스트렙토코쿠스_인판티스	서열 번호 286	GACGAACGCTGGCGGCGTGCCTAATACATGCAAGTAGAACGCTGAAGGAGGAGCTTG CTCTTCTGGATGAGTTGCGAACGGGTGAGTAACGCGTAGGTAACCTGCCTGGTAGCG GGGGATAACTATTGGAAACGATAGCTAATACCGCATAACAGTAGATATCGCATGATA GCTGCTTGAAAGGTGCAATTGCACCACTACCAGATGGACCTGCGTTGTATTAGCTAGT TGGTGAGGTAACGGCTCACCAAGGCAACGATACATAGCCGACCTGAGAGGGTGATCG GCCACACTGGGACTGAGACACGGCCCAGACTCCTACGGGAGGCAGCAGTAGGGAAT CTTCGGCAATGGACGGAAGTCTGACCGAGCAACGCCGCGTGAGTGAAGAAGGTTTTC GGATCGTAAAGCTCTGTTGTAAGAGAAGAACGAGTGTGAGAGTGGAAAGTTCACACT GTGACGGTATCTTACCAGAAAGGGACGGCTAACTACGTGCCAGCAGCCGCGGTAATA CGTAGGTCCCGAGCGTTGTCCGGATTTATTGGGCGTAAAGCGAGCGCAGGCGGTTAG ATAAGTCTGAAGTTAAAGGCTGTGGCTTAACCATAGTACGCTTTGGAAACTGTTTAAC TTGAGTGCAAGAGGGGAGAGTGGAATTCCATGTGTAGCGGTGAAATGCGTAGATATA TGGAGGAACACCGGTGGCGAAAGCGGCTCTCTGGCTTGTAACTGACGCTGAGGCTCG AAAGCGTGGGGAGCAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGA GTGCTAGGTGTTAGACCCTTTCCGGGGTTTAGTGCCGAAGCTAACGCATTAAGCACTC CGCCTGGGGAGTACGACCGCAAGGTTGAAACTCAAAGGAATTGACGGGGGCCCGCA CAAGCGGTGGAGCATGTGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAGGTCTT GACATCCCTCTGACCGCTCTAGAGATAGAGTTTTCCTTCGGGACAGAGGTGACAGGT GGTGCATGGTTGTCGTCAGCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAACGAGC GCAACCCCTATTGTTAGTTGCCATCATTTAGTTGGGCACTCTAGCGAGACTGCCGGTA ATAAACCGGAGGAAGGTGGGGATGACGTCAAATCATCATGCCCCTTATGACCTGGGC TACACACGTGCTACAATGGTTGGTACAACGAGTCGCAAGCCGGTGACGGCAAGCTAA TCTCTTAAAGCCAATCTCAGTTCGGATTGTAGGCTGCAACTCGCCTACATGAAGTCGG AATCGCTAGTAATCGCGGATCAGCACGCCGCGGTGAATACGTTCCCGGGCCTTGTAC ACACCGCCCGTCACACCACGAGAGTTTGTAACACCCGAAGTCGGTGAGGTAACCATT TGGAGCCAGCCGCCTAAGGTGGGATAGATGATT
클로스트리듐_속_CL_6	서열 번호 287	GCGATGAAGCCCTTCGGGGTGGATTAGCGGCGGACGGGTGAGTAACACGTGGGTAAC CTGCCTTGTAGAGGGGGATAGCCTTCCGAAAGGAAGATTAATACCGCATAACATCTT TTTATCGCATGGTAGAAAGATCAAAGGAGCAATCCGCTACAAGATGGACCCGCGGCG CATTAGCTAGTTGGTGAGGTAACGGCTCACCAAGGCGACGATGCGTAGCCGACCTGA GAGGGTGATCGGCCACATTGGAACTGAGACACGGTCCAGACTCCTACGGGAGGCAGC AGTGGGGAATATTGCGCAATGGGGGAAACCCTGACGCAGCAACGCCGCGTGAATGA AGAAGGCCTTAGGGTTGTAAAGTTCTGTTTACGGGGACGATAATGACGGTACCCGTG GGGAAGCCACGGCTAACTACGTGCCAGCAGCCGCGGTAATACGTAGGTGGCAAGCGT TGTCCGGATTTACTGGGCGTAAAGGATGCGTAGGCGGATGTTTAAGTGAGATGTGAA ATACCCGGGCTCAACTTGGGTGCTGCATTTCAAACTGGACATCTAGAGTGCGGGAGA GGAAAGCGGAATTCCTAGTGTAGCGGTGAAATGCGTAGAGATTAGGAAGAACACCA GTGGCGAAGGCGGCTTTCTGGACCGTAACTGACGCTGAGGCATGAAAGCGTGGGGAG CAAACAGGATTAGATACCCTGGTAGTCCACGCCGTAAACGATGAATACTAGGTGTAG GAGGTATCGACTCCTTCTGTGCCGCAGTTAACACAATAAGTATTCCGCCTGGGAAGTA CGATCGCAAGATTAAAACTCAAAGGAATTGACGGGGGCCCGCACAAGCAGCGGAGC ATGTGGTTTAATTCGAAGCAACGCGAAGAACCTTACCTAGACTTGACATCTCCTGAAT

[0226]

		TACTCTTAATCGAGGAAGCCCTTCGGGGCAGGAAGACAGGTGGTGCATGGTTGTCGT CAGCTCGTGTCGTGAGATGTTGGGTTAAGTCCCGCAACGAGCGCAACCCTTATCATTA GTTGCTACCATTAAGTTGAGCACTCTAGTGAGACTGCCACGGTTAACGTGGAGGAAG GTGGGGATGACGTCAAATCATCATGCCCCTTATGTCTAGGGCTACACACGTGCTACAA TGGTGAATACAAATAGATGCAATACCGCGAGGTGGAGCCAAACTATAAAATTCATCC CAGTTCGGATTGCAGTCTGAAACTCGACTGCATGAAGCCGGAGTTGCTAGTAATCGC GAATCAGCATGTCGCGGTGAATACGTTCCCGGGCCTTGTACACACCGCCCGTCACACC ATGAGAGCTGGTAACACCCGAAGTTCCGTGAGGTAACCGCA

[0227]

표 6 – 종의 전장 16S rDNA 서열 (양의 상관관계)

종 명	서열 식별자	16S 서열
스트렙토코루스_미티스_오랄리스_뉴모니아	서열 번호 288	aatgagagtttgatcctggctcaggacgaacgctggcggcgtgcctaatacatgcaagtagaacgctgaaggaggagcttgcttctctggatgagtt gcgaacgggtgagtaacgcgtaggtaacctgcctggtagcgggggataactattggaaacgatagctaataccgcataagagtggatgttgcatga catttgcttaaaaggtgcacttgcatcactaccagatggacctgcgttgtattagctagttggtggggtaacggctcaccaaggcgacgatacatagcc gacctgagagggtgatcggccacactgggactgagacacggcccagactcctacgggaggcagcagtagggaatcttcggcaatggacggaag tctgaccgagcaacgccgcgtgagtgaagaaggttttcggatcgtaaagctctgttgtaagagaagaacgagtgtgagagtggaaagttcacactgt gacggtatcttaccagaaagggacggctaactacgtgccagcagccgcggtaatacgtaggtcccgagcgttgtccggatttattgggcgtaaagc gagcgcaggcggttagataagtctgaagttaaaggctgtggctaaccatagtaggctttggaaactgtttaacttgagtgcaagagggagagtgg aattccatgtgtagcggtgaaatgcgtagatatatggaggaacaccggtggcgaaagcggctctctggcttgtaactgacgctgaggctcgaaagc gtggggagcaaacaggattagataccctggtagtccacgctgtaaacgatgagtgctaggtgttagacccttccggggtttagtgccgtagctaacg cattaagcactccgcctggggagtacgaccgcaaggttgaaactcaaaggaattgacgggggcccgcacaagcggtggagcatgtggtttaattc gaagcaacgcgaagaacctaccaggtcttgacatccctctgaccgctctagagatagagttttccttcgggacagaggtgacaggtggtgcatggtt gtcgtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaaccctattgttagttgccatcattcagttgggcactctagcgagactg ccggtaataaaccggaggaaggtggggatgacgtcaaatcatcatgccccttatgacctgggctacacacgtgctacaatggctggtacaacgagt cgcaagccggtgacggcaagctaatctcttaaagccagtctcagttcggattgtaggctgcaactcgcctacatgaagtcggaatcgctagtaatcgc ggatcagcacgccgcggtgaatacgttcccgggccttgtacacaccgcccgtcacaccacgagagtttgtaacacccgaagtcggtgaggtaacc gtaaggagccagccgcctaaggtgggatagatgattggggtgaagtcgtaacaaggtagccgtatcggaaggtgcggctggatcacctcctt	
스트렙토코루스_미티스_오랄리스_뉴모니아	서열 번호 289	aatgagagtttgatcctggctcaggacgaacgctggcggcgtgcctaatacatgcaagtagaacgctgaaggaggagcttgcttctctggatgagtt gcgaacgggtgagtaacgcgtaggtaacctgcctggtagcgggggataactattggaaacgatagctaataccgcataagagtggatgttgcatga catttgcttaaaaggtgcacttgcatcactaccagatggacctgcgttgtattagctagttggtggggtaacggctcaccaaggcgacgatacatagcc gacctgagagggtgatcggccacactgggactgagacacggcccagactcctacgggaggcagcagtagggaatcttcggcaatggacggaag tctgaccgagcaacgccgcgtgagtgaagaaggttttcggatcgtaaagctctgttgtaagagaagaacgagtgtgagagtggaaagttcacactgt gacggtatcttaccagaaagggacggctaactacgtgccagcagccgcggtaatacgtaggtcccgagcgttgtccggatttattgggcgtaaagc gagcgcaggcggttagataagtctgaagttaaaggctgtggctaaccatagtaggctttggaaactgtttaacttgagtgcaagaggggagagtgg aattccatgtgtagcggtgaaatgcgtagatatatggaggaacaccggtggcgaaagcggctctctggcttgtaactgacgctgaggctcgaaagc gtggggagcaaacaggattagataccctggtagtccacgctgtaaacgatgagtgctaggtgttagacccttccggggtttagtgccgtagctaacg cattaagcactccgcctggggagtacgaccgcaaggttgaaactcaaaggaattgacgggggcccgcacaagcggtggagcatgtggtttaattc gaagcaacgcgaagaacctaccaggtcttgacatccctctgaccgctctagagatagagttttccttcgggacagaggtgacaggtggtgcatggtt gtcgtcagctcgtgtcgtgagatgttgggttaagtcccgcaacgagcgcaaccctattgttagttgccatcattcagttgggcactctagcgagactg ccggtaataaaccggaggaaggtggggatgacgtcaaatcatcatgccccttatgacctgggctacacacgtgctacaatggctggtacaacgagt cgcaagccggtgacggcaagctaatctcttaaagccagtctcagttcggattgtaggctgcaactcgcctacatgaagtcggaatcgctagtaatcgc ggatcagcacgccgcggtgaatacgttcccgggccttgtacacaccgcccgtcacaccacgagagtttgtaacacccgaagtcggtgaggtaacc gtaaggagccagccgcctaaggtgggatagatgattggggtgaagtcgtaacaaggtagccgtatcggaaggtgcggctggatcacctcctt	
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[0254]

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[0255]

[0256] 실시예 3: 인간 연구 - 궤양성 대장염

[0257] 중등도의 궤양성 대장염을 앓고 있는 인간 대상체는 위약 단독 (중재군 A), 건강한, 선별된 인간의 배설물에서 제조된 강화하고 정제된 포자의 매주 복용 (중재군 B), 짧은 코스의 반코마이신에 이어 포자의 매주 투여 (중재군 D), 또는 짧은 코스의 반코마이신에 이어 포자의 매일 투여 (중재군 C)를 받는다.

[0258] 항생제가 궤양성 대장염 치료의 표준이 아니기 때문에, 이 대상체 집단은 반복 재발성 C. 디피실리 집단 (상기 실시예 1)과 비교하여 항생제로 자주 치료받을 가능성이 낮다. 따라서, 궤양성 대장염 대상체의 마이크로바이옴은 항생제 내성에 대해 강력한 선택 기간이 더 적었다. 항생제 전 기준선 샘플 (방문 1, 도 3)에서, 본 출원

인은 항생제 내성 유전자의 낮은 존재비를 관찰하였다.

[0259] 결과는 AbxR 유전자 존재비가 항생제 후 기준선 샘플 (방문 4, 8일)과 비교하여 처리 후 시점에서 더 낮음을 보여준다. 중재군 C 및 D에서, 반코마이신으로 처리하면 치료 후 항생제 내성 유전자가 급격히 상승한다 (방문 4, 8일). 매일 또는 매주 포자 치료는 항생제 후 기준선 (방문 4, 표 7)에 비해 방문 5 (15일, 투여 개시 후 7일)에서 항생제 내성 유전자의 유의한 감소를 유발한다.

표 7. AbxR 유전자 존재비는 항생제 후 기준선 샘플과 비교하여 선택된 처리 후 시점에서 더 낮음 (방문 4, 8 일).

	중재군	11 일 (처리 후 3 일) < 8 일 (반코마이신 후)	15 일 (처리 후 7 일) < 8 일 (반코마이신 후)
윌콕스 검정 p-값 (단측 쌍체 검정)	D (반코마이신 후 매주 포자)	0.01367	0.03223
윌콕스 검정 p-값 (단측 쌍체 검정)	C (반코마이신 후 매일 포자)	0.6562	0.009766

[0260]

[0261] AbxR 유전자 존재비는 항생제 전 기준 샘플 (방문 1)과 비교하여 처리 후 시점에서 낮다. 중재군 C 및 D에서, 포자 처리는 항생제 전 기준 샘플 (방문 1, 표 8, 도 3)과 비교하여 항생제 내성 유전자 감소를 유발한다. 매일 포자 처리는 항생제 전 기준 샘플 (방문 1, 표 8)과 비교하여 방문 5 및 방문 6 (각각, 18일, 28일)에서 항생제 내성 유전자의 유의한 감소를 유발한다.

표 8. 포자 처리는 항생제 전 기준선과 비교하여 AbxR 유전자 존재비의 감소를 유발하였음 (예를 들어 방문 1(항생제 전) 대 (방문 5 또는 방문 6)).

	중재군	방문 5 (18 일)	방문 6
윌콕스 검정 p-값 (단측 쌍체 검정)	D (반코마이신 후 매주 포자)	0.1826	0.1902
윌콕스 검정 p-값 (단측 쌍체 검정)	C (반코마이신 후 매일 포자)	0.01367	0.04199

[0262]

[0263] 결과는 포자의 생착이 항생제 내성을 감소시킨다는 것을 보여준다. 중재군 D (매주 투약)에서, 포자는 대상체의 서브셋에서 빠르게 생착되었다 (신속 조기 생착자 = 참, 도 4). 나머지 대상체에서 생착은 규모나 시기가 감소했다 (신속 조기 생착자 = 거짓, 도 4). "신속 조기 생착자"는 방문 5 (15일)에 검출된 6 초과의 투약된 포자 형성제가 있는 대상체로 정의하였다. 본 출원인은 이러한 신속한 조기 생착 대상체가 방문 5 (15일, 포자의 제 1 투약 후 7일)에 빠른 초기 생착자로 확인되지 않은 것들과 비교하여 방문 5 (15일)에 현저하게 낮은 AbxR 유전자 존재비를 나타냄을 관찰하였다.

표 9. 동일 시점내 AbxR 유전자 존재비는 비신속 생착자, 중재군 D(매주 투약)에 비해 신속 생착자에서 낮음.

	8 일 (처리 전)	11 일 (처리 후 3 일)	15 일 (처리 후 6 일)
윌콕스 검정 p-값 (대안="미만")	0.6548	0.3312	0.07343

[0264]

[0265] 실시예 4: 동물 모델

[0266] 항생제 내성을 감소시키는 능력에 대한 ROAR 조성물을 시험하는 한 가지 방법은 통상적인 마우스 (마이크로바이옴을 갖는 실험실 균주)를 사용한다. 선택된 항생제로 마우스를 처리한 후, 하나 이상의 항생제 내성 유전자, 예를 들어 반코마이신 내성 장구균 (vancomycin resistant Enterococcus; VRE) 또는 반코마이신 및 카바페넴 내성 장내 세균 (carbapenem resistant Enterobacteriaceae; CRE)를 보유하는 세균으로 콜로니화한다. 콜로니화 후, 마우스를 ROAR 조성물, 분변 이식 또는 대조군으로 처리하였다. 항생제 내성 세균의 역가 (예를 들어, 반코마이신 내성 및 카바페넴 내성 세균)를 처리된 동물로부터 수집된 대변의 플레이팅을 통해 모니터링한다.

[0267] 출원인은 공개된 모델 (Caballero and Pamer, 2015, Ann Rev Immunol 33:227-256)을 기초로 하여 마우스에서 재현성있고 탄탄한 반코마이신-내성 장구균 (VRE) 콜로니화 모델을 확립하였다. VRE 접종 전에, 특정 병원체 유리 (SPF) 마우스는 콜로니 내성을 파괴하고 VRE 콜로니화를 허용하기 위해 암피실린으로 사전 조절된다. 암피실린 처리 후, 마우스를 VRE로 챌린지시키고 GI 관에서 높은 역가 (10^7 내지 10^{10} CFU/g 배설물) 캐리지를 달성하고, 이는 수 주 동안 안정한 상태이다. VRE로 콜로니화되면, 마우스를 3일 동안 매일 경구 위관 영양법을 통해 인간 FMT 또는 ROAR 내성 조성물로 처리한다. 마우스로부터 VRE를 제거하고 건강한 장내 미생물을 회복시키는 조성물의 능력을 평가하기 위해 연구 전반에 걸쳐 신선한 배설물 샘플을 수집하였다. 처리 전 및 처리 후 배설물에서의 VRE 생존 역가는 반코마이신 및 스트렙토마이신을 갖는 담즙 에스쿨린 아지드 한천을 함유하는 선택적 배지 상에 플레이팅함으로써 측정한다. VRE 콜로니 모델은 PBS로만 처리된 마우스와 비교하여 인간 FMT로 처리된 마우스에서 3주에 걸친 콜로니화의 >4 로그 차이를 검출할 수 있다. 연구 기간 동안 VRE 역가에서 >4 로그 차이를 검출하는 능력은 또한 차등 효능을 갖는 설계된 미생물 조성물을 구별하였다. 또한, 항생제 내성 유전자의 존재비를 분석할 수 있다. CRE에 적합한 선택적 배지를 대체하여, 카바페넴 내성 장내 세균 (CRE) 내성을 비슷한 방식으로 시험할 수 있다.

[0268] 이러한 모델을 사용하여, 항생제 내성 유전자의 존재비에 대한 ROAR 조성물의 효과를 시험할 수 있다. 이러한 모델에서 하나 이상의 항생제 내성 유전자의 존재비를 감소시킬 수 있는 ROAR 조성물은 본원에 기재된 방법에 대해 유용하다.

[0269] 본 발명의 다양한 양태는 하기 번호가 매겨진 절 내에 존재한다.

[0270] 1. 대상체의 마이크로바이옴에서, 적어도 하나의 항생제 내성 유전자의 존재비를 감소시키는 방법으로서, 치료적 유효량의 포자-형성자 세균을 포함하는 마이크로바이옴 조성물을 투여하는 것을 포함하는 방법.

[0271] 2. 바람직하지 못한 수준 또는 집단의 약물 내성 세균을 가질 위험이 있거나 가진 것으로 진단된 대상체를 치료하는 방법으로서, 방법은 하나 이상의 건강한 인간 대상체로부터 유래된 후벽균을 포함하는 치료적 유효량의 마이크로바이옴 조성물을 투여하는 것을 포함하는 방법.

[0272] 3. 대상체의 마이크로바이옴에서 항생제 내성 세균의 존재비를 감소시키는 방법으로서, 치료적 유효량의 ROAR 조성물을 투여하는 것을 포함하는 방법.

[0273] 4. 항생제 내성 유전자의 전달 주기를 방해하는 방법으로서, 체액 또는 노폐물과의 접촉을 포함하여 직접 또는 간접적으로 접촉할 가능성이 큰 적어도 2 명의 개체에게 ROAR 조성물을 투여하는 것을 포함하는 방법.

[0274] 5. 절 1에 있어서, 항생제 내성 유전자(들)이 표 1에 열거된 것들로부터 선택되는 방법.

[0275] 6. 절 5에 있어서, 표 1의 2, 3, 4, 5, 6, 7, 8, 9, 10개 또는 그 초과의 항생제 내성 유전자의 존재비가 감소되는 방법.

[0276] 7. 절 1 내지 6 중 어느 한 절에 있어서, 약물 또는 항생제가 표 2에 열거된 약물 종류로부터 유래된 방법.

[0277] 8. 절 1 내지 절 7 중 어느 한 절에 있어서, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25개 또는 그 초과의 항생제 내성 유전자 또는 약물 종류의 존재비를 감소시키는 단계를 추가로 포함하는 방법.

[0278] 9. 절 1 내지 8 중 어느 한 절에 있어서, 투여된 조성물은 표 3에 열거된 하나 이상의 종을 포함하는 방법.

[0279] 10. 절 9에 있어서, 투여된 조성물이 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함하는 방법.

[0280] 11. 절 9 또는 10에 있어서, 투여된 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는 방법.

[0281] 12. 절 1 내지 11 중 어느 한 절에 있어서, 투여된 조성물은 표 4의 하나 이상의 종을 포함하지 않는 방법.

[0282] 13. 절 1 내지 12 중 어느 한 절에 있어서, 조성물 중 세균이 포자의 형태인 방법.

[0283] 14. 절 1 내지 13 중 어느 한 절에 있어서, 조성물 중의 세균이 배양되는 방법.

[0284] 15. 절 1 내지 14 중 어느 한 절에 있어서, 상기 조성물은 후벽균 및 하나 이상의 박테로이데스 종을 포함하는 방법.

[0285] 16. 절 1 내지 15 중 어느 한 절에 있어서, 대상체는 퀴놀론 내성, 베타-락탐 내성 및 카바페넴 내성 세균으로 이루어진 군으로부터 선택된 1, 2 또는 3개의 세균의 감소된 존재비를 가지는 방법

[0286] 17. 절 1 내지 16 중 어느 한 절에 있어서, 대상체가 항생제 치료에 반응하지 않는 방법.

[0287] 18. 절 1 내지 17 중 어느 한 절에 있어서, 대상체가 *C. 디피실리* 감염이 있거나 발병할 위험이 있는 방법.

[0288] 19. 절 1 내지 18 중 어느 한 절에 있어서, 대상체가 대장염을 앓거나 발병할 위험이 있는 방법.

[0289] 20. 절 19에 있어서, 대장염이 크론병 또는 궤양성 대장염인 방법.

[0290] 21. 절 20에 있어서, 대장염이 경증 내지 중등도의 궤양성 대장염인 방법.

[0291] 22. 대상체에서 적어도 하나의 항생제 내성 유전자의 존재비 감소와 관련된 세균 종을 포함하는 조성물.

[0292] 23. 절 22에 있어서, 항생제-내성 유전자(들)가 표 1에 열거된 것들로부터 선택되는 조성물.

[0293] 24. 절 23에 있어서, 표 1의 2, 3, 4, 5, 6, 7, 8, 9, 10개 또는 그 초과의 항생제 내성 유전자의 존재비가 감소되는 조성물.

[0294] 25. 절 22 내지 24 중 어느 한 절에 있어서, 항생제는 표 2에 열거된 종류인 조성물.

[0295] 26. 절 22 내지 25 중 어느 한 절에 있어서, 조성물은 표 3에 열거된 하나 이상의 종을 포함하는 조성물.

[0296] 27. 절 26에 있어서, 조성물은 표 3에 열거된 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20개 또는 그 초과의 종을 포함하는 조성물.

[0297] 28. 절 20 또는 27에 있어서, 종은 표 5에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는 조성물.

[0298] 29. 절 22 내지 28 중 어느 한 절에 있어서, 조성물은 표 4의 하나 이상의 종을 포함하지 않고, 선택적으로 표 4의 하나 이상의 종은 표 6에서 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는 조성물.

[0299] 30. 절 22 내지 29 중 어느 한 절에 있어서, 조성물은 하나 이상의 종의 후벽군을 포함하는 조성물.

[0300] 31. 절 22 내지 30 중 어느 한 절에 있어서, 조성물은 하나 이상의 종의 박테로이데스를 포함하는 조성물.

[0301] 32. 절 22 내지 31 중 어느 한 절에 있어서, 조성물 중의 세균은 포자의 형태인 조성물.

[0302] 33. 절 22 내지 32 중 어느 한 절에 있어서, 조성물 중 세균은 건강한 대상의 배설물로부터 유래된 포자 분획으로부터 수득되는 조성물.

[0303] 34. 절 22 내지 33 중 어느 한 절에 있어서, 조성물은 하나 이상의 후벽균 종, 및 선택적으로 하나 이상의 박테로이데스 종을 조성물 중의 유일한 세균 종으로 포함하는 조성물.

[0304] 35. 절 22 내지 34 중 어느 한 절에 있어서, 조성물 중의 세균이 배양되는 조성물.

[0305] 36. 조성물이 투여되는 대상체에서 하나 이상의 항생제 내성 유전자의 존재비를 감소시키는 데 사용하기 위한 세균을 포함하는 조성물.

[0306] 37. 절 36에 있어서, 조성물 중 세균이 건강한 대상의 배설물로부터 유래된 포자 분획으로부터 수득되는 조성물.

[0307] 38. 절 36에 있어서, 세균이 대상체에서 하나 이상의 항생제 내성 유전자의 존재 감소와 관련되도록 선택되는 절 36의 조성물.

[0308] 39. 절 36 내지 38 중 어느 한 절에 있어서, 항생제 내성 유전자(들)은 표 1로부터 선택되는 조성물.

[0309] 40. 절 36 내지 39 중 어느 한 절에 있어서, 조성물은 표 3에서 선택된 적어도 하나의 종을 포함하는 조성물.

[0310] 41. 절 36 내지 40 중 어느 한 절에 있어서, 조성물은 표 4의 종을 포함하지 않는 조성물.

[0311] 42. 조성물이 투여되는 대상체에서 하나 이상의 항생제 내성 유전자의 존재비를 감소시키는 데 유용한 세균 조성물을 확인하는 방법에 있어서, 표 3의 하나 이상의 세균 종의 존재에 대해 조성물을 스크리닝하는 단계를 포함하고, 세균 조성물에서 표 3의 하나 이상의 종의 검출은 하나 이상의 항생제 내성 유전자의 존재비를 감소시키기 위해 사용될 수 있는 조성물의 확인을 나타내는 방법.

[0312] 43. 절 42에 있어서, 스크리닝은 조성물에서 표 5의 하나 이상의 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열의 검출을 포함하는 방법.

[0313] 44. 절 42 또는 43에 있어서, 표 4의 하나 이상의 세균 종의 존재에 대한 스크리닝을 추가로 포함하고, 선택적으로 표 4의 하나 이상의 종은 표 6에 열거된 16S rDNA, V4 및/또는 V6 서열, 또는 이에 대해 적어도 95% 동일성을 갖는 서열을 포함하는 방법.

[0314] 45. 치료적 방법에 사용하기 위한 잠재적 공여자를 스크리닝하는 방법으로서, 표 3 또는 표 4의 세균 종의 존재에 대해 잠재적 공여자로부터의 배설물 샘플을 시험하는 단계를 포함하고, 표 3으로부터의 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 될 수 있음을 나타내고, 표 4로부터 하나 이상의 종의 검출은 잠재적 공여자가 공여자가 되지 않아야 함을 나타내는 방법.

[0315] 46. 대상체가 ROAR 조성물로 치료함으로써 이익을 얻을 수 있는지를 결정하는 방법으로서, 대상체로부터의 샘플이 표 4의 하나 이상의 세균 종을 포함하는지를 결정하는 단계를 포함하고, 표 4로부터 하나 이상의 종의 검출은 대상체가 ROAR 조성물로 치료함으로써 이익을 얻을 수 있다는 점을 나타내는 방법.

[0316] 47. 절 22 내지 41 중 어느 한 절에 있어서, 조성물 중의 세균은 항생제 내성의 동물 모델에서 하나 이상의 항생제 내성 유전자(들)의 존재비를 감소시키는 능력을 나타내는 조성물.

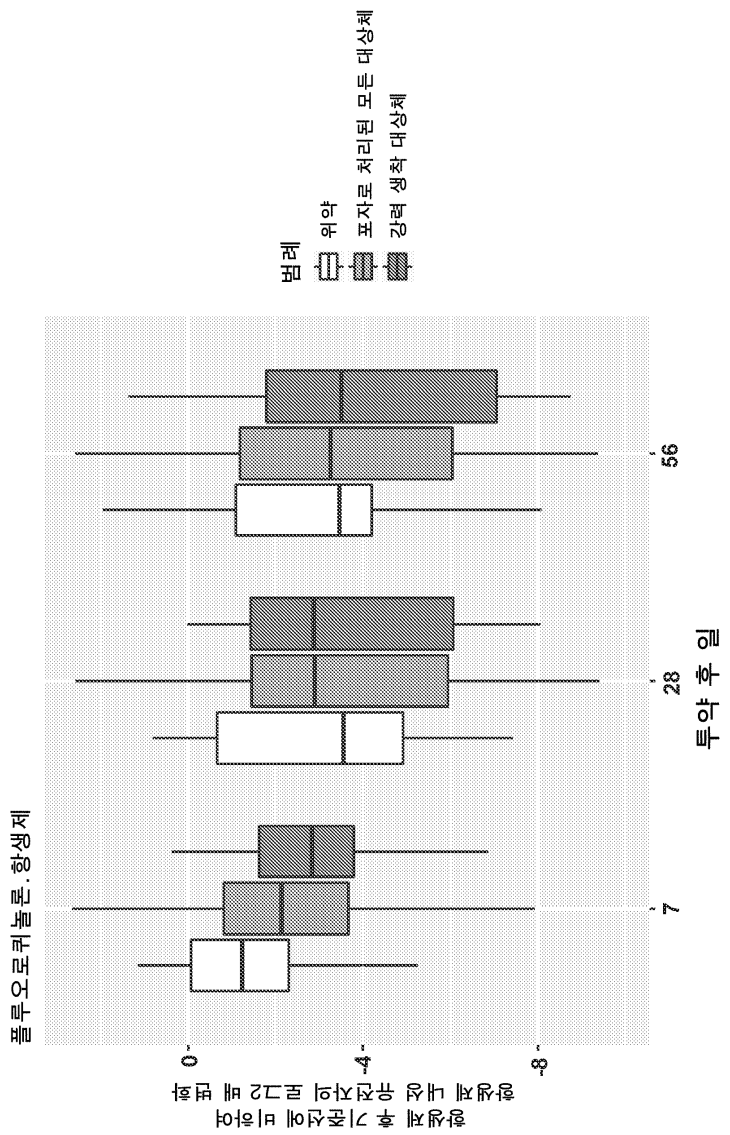
[0317] 48. 절 47에 있어서, 동물 모델이 하나 이상의 항생제로 처리된 후 하나 이상의 항생제 내성 유전자를 보유하는 하나 이상의 세균으로 콜로니화된 마우스를 포함하는 조성물.

[0318] 49. 절 48에 있어서, 마우스는 반코마이신 내성 세균 또는 반코마이신 및 카바페넴 내성 세균으로 콜로니화되는 조성물.

[0319] 다른 양태는 하기 청구항의 범위 내에 존재한다.

도면

도면1


범례
위약
포자로 처리된 모든 대상체
강력 생착 대상체
플루오로퀴놀론-항생제
0
-4
-8
항생제 후 기준선에 비하여
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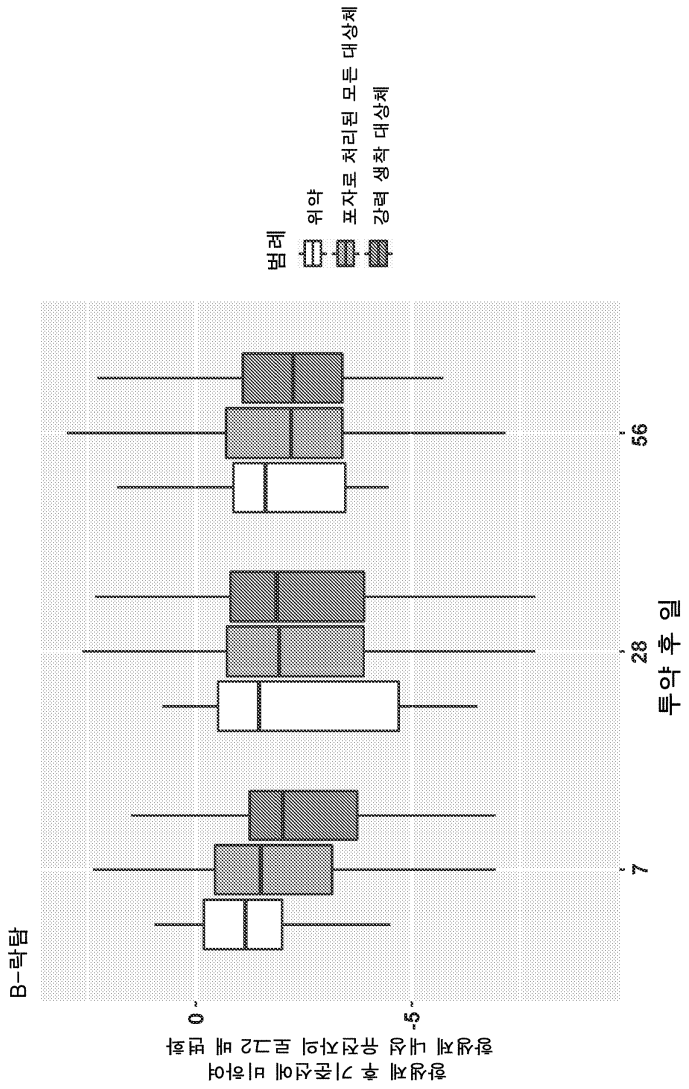
도면2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강력 생착 대상체
B-락탐
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항생제 후 기준선에 비하여
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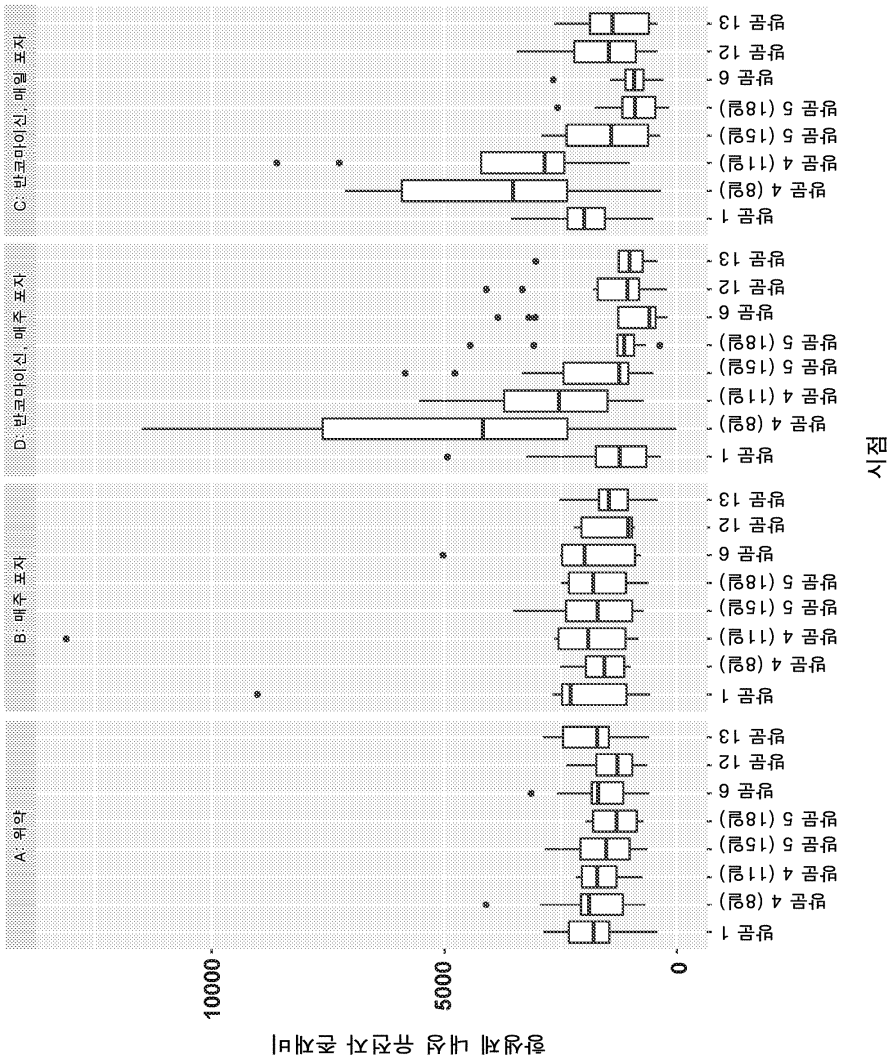
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방문 1
방문 4 (8일)
방문 4 (11일)
방문 5 (15일)
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시점

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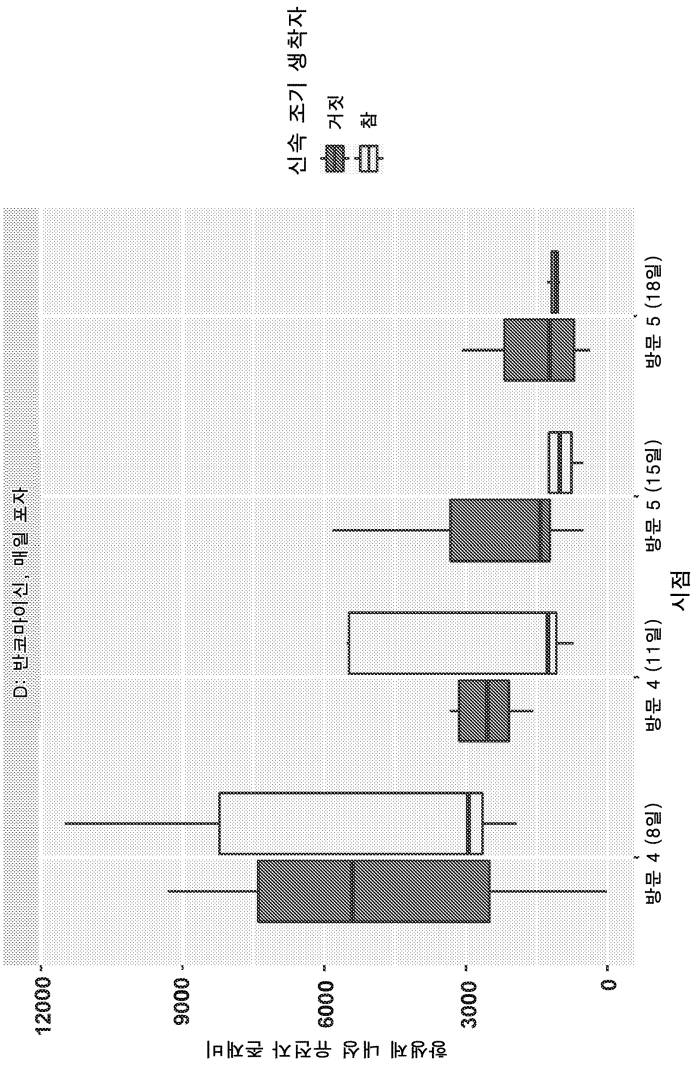

서 열 목 록

<110> Seres Therapeutics, Inc.

<120> COMPOSITIONS AND METHODS FOR TREATING ANTIBIOTIC RESISTANCE

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<213> Clostridium_sp.

<400> 10

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aacgaagttg ctttgaatga attcttcgga aggaatttga ttcaacttag tggcggacgg 120

gtgagtaacg cgtgagtaac ctgcctttca gaggggggata acgtctggaa acggacgcta 180

ataccgcata acatattggt ttcgcatgga gctgatatca aaggagcaat ccgctgaaag 240

atggactcgc gtccaattag ctagttggtg aggtaacggc ccaccaaggc gacgattggt 300

agccggactg agaggttgaa cggccacatt gggactgaga cacggcccag actcctacgg 360

gaggcagcag tggggaatat tgcacaatgg gggaaaccct gatgcagcga cgccgagtga 420

gggaagaagg ttttcggatt gtaaacctct gtccttggtg aagataatga cggtaaccaa 480

ggaggaagct acggctaact acgtgccagc agccgcggta atacgtaggt agcgagcgtt 540

gtccggaatt actgggtgta aagggagcgt aggcgggatt gcaagttgaa tgttaaatct 600

atgggctcaa cccatagccg cgttcaaaac tgcagttctt gagtgaagta gaggcaggcg 660

gaattcctag tgtagcggtg aaatgcgtaa atattaggag gaacaccagt ggcgaaggcg 720

gcctgctggg ctttaactga cgctgaggct cgaaagcgtg ggtagcaaac aggattagat 780

accctggtag tccacgctgt aaacgatgat tactaggtgt gggggactg acccttccg 840

tgccggagtt aacacaataa gtaatccacc tggggagtac gaccgcaagg ttgaaactca 900

aaggaattga cgggggcccg cacaagcagt ggagtatgtg gtttaattcg aagcaacgcg 960

aagaacctta ccaggtcttg acatccggtg catagcctag agataggtga agcccttcgg 1020

ggcaccgaga caggtggtgc atggttgtcg tcagctcgtg tcgtgagatg ttgggttaag 1080

tcccgcaacg agcgcaaccc ttacgtttag ttgctacgca agagcactct agacggactg 1140

ccgttgacaa aacggaggaa ggtggggatg acgtcaaatc atcatgcccc ttatgacctg 1200

ggctacacac gtactacaat ggctattaac agagggaagc aagatggtga catggagcaa 1260

acccctaaaa atagtctcag ttcggattgc aggctgcaac ccgcctgcat gaagccggaa 1320

ttgctagtaa tcgcggatca gcatgccgcg gtgaatacgt tcccgggcct tgtacacacc 1380

gcccgtcaca ccatgagagt tggcaacacc cgaagccgat agtctaaccg caaggggggac 1440

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gtgcggctgg atcacctcct tt 1522

<210> 11

<211> 1515

<212> DNA

<213> Clostridium_sp.

<400> 11

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aacggaattt acatgaagcc tagcgattgt aaatttagtg gcggacgggt gagtaacgcg 120

tgggtaacct gccttgtact gggggacaac agttggaaac gactgctaat accgcataag 180

cgcacagctt cgcatgaagc agtgtgaaaa actccggtgg tacaagatgg acccgcgtct 240

gattagctgg ttggtgaggt aacggcccac caaggcgacg atcagtagcc ggcctgagag 300

ggtgaacggc cacattggga ctgagacacg gcccaaactc ctacgggagg cagcagtggg 360

gaatattgca caatggggga aaccctgatg cagcaacgcc gcgtgagtga agaagtattt 420

cggtatgtaa agctctatca gcaggaaaga aaatgacggt acctgactaa gaagccccgg 480

ctaactacgt gccagcagcc gcggtaatac gtaggggcga agcgttatcc ggatttactg 540

ggtgtaaagg gagcgtagac ggttttgcaa gtctgaagtg aaagcccggg gcttaacccc 600

gggactgctt tggaaactgt aggactagag tgcaggagag gtaagtggaa ttcctagtgt 660

agcggtgaaa tgcgtagata ttaggaggaa caccagtggc gaaggcggct tactggactg 720

taactgacgt tgaggctcga aagcgtgggg agcaaacagg attagatacc ctggtagtcc 780

acgccgtaaa cgatgattac taggtgttgg tgggtacgac ccatcggtgc cgcagcaaac 840

gcaataagta atccacctgg ggagtacgtt cgcaagaatg aaactcaaag gaattgacgg 900

ggacccgcac aagcggtgga gcatgtggtt taattcgaag caacgcgaag aaccttacct 960

ggtcttgaca tccctatgaa taacgggcaa tgccgttagt acttcggtac ataggagaca 1020

ggtggtgcat ggttgtcgtc agctcgtgtc gtgagatgtt gggttaagtc ccgcaacgag 1080

cgcaaccctt atctttagta gccagcagta agatgggcac tctagagaga ctgccgggga 1140

taacccggag gaaggtgggg atgacgtcaa atcatcatgc cccttatgac cagggctaca 1200

cacgtgctac aatggcgtaa acaaagagaa gcgaagtcgt gaggcagagc gaatctcaaa 1260

aataacgtct cagttcggat tgtagtctgc aactcgacta catgaagctg gaatcgctag 1320

taatcgcaga tcagaatgct gcggtgaata cgttcccggg tcttgtacac accgcccgtc 1380

acaccatggg agtcggaaat gcccgaagtc ggtgacctaa ccgaaaggaa ggagccgccg 1440

aaggcaggtc tgataactgg ggtgaagtcg taacaaggta gccgtatcgg aaggtgcggc 1500

tggatcacct ccttt 1515

<210> 12

<211> 1558

<212> DNA

<213> Clostridium_sp.

<220><221> misc_feature

<222> (992)..(1038)

<223> n is a, c, g, or t

<400> 12

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aacgaggtat tttgattgaa gttttcggat ggatttcaag ataccgagtg gcggacgggt 120

gagtaacgcg tgggtaacct gcctcataca gggggataac ggttagaaat gactgctaat 180

accgcataag cgcacagtac cgcatggtac ggtgtgaaaa actccggtgg tatgagatgg 240

acccgcgtct gattagctag ttggtggggt aacggcccac caaggcgacg atcagtagcc 300

gacctgagag ggtgaccggc cacattggga ctgagacacg gcccagactc ctacgggagg 360

cagcagtggg ggatattgca caatggagga aactctgatg cagcgacgcc gcgtgagtga 420

agaagtattt cggtatgtaa agctctatca gcagggaaga aaatgacggt acctgactaa 480

gaagccccgg ctaactacgt gccagcagcc gcggtaatac gtaggggcca agcgttatcc 540

ggatttactg ggtgtaaagg gagcgtagac ggcgacgcaa gtctgaagtg aaatacccgg 600

gctcaacctg ggaactgctt tggaaactgt gttgctagag tgctggagag gtaagcggaa 660

ttcctagtgt agcggtgaaa tgcgtagata ttaggaagaa caccagtggc gaaggcggct 720

tactggacag taactgacgt tgaggctcga aagcgtgggg agcaaacagg attagatacc 780

ctggtagtcc acgccgtaaa cgatgaatac taggtgttgg tgagcaaagc tcatcggtgc 840

cgccgcaaac gcaataagta ttccacctgg ggagtacgtt cgcaagaatg aaactcaaag 900

gaattgacgg ggacccgcac aagcggtgga gcatgtggtt taattcgaag caacgcgaag 960

aaccttacca aatcttgaca tccctctgaa annnnnnnnn nnnnnnnnnn nnnnnnnnnn 1020

nnnnnnnnnn nnnnnnnncc tccttcggga cagaggtgac aggtggtgca tggttgtcgt 1080

cagctcgtgt cgtgagatgt tgggttaagt cccgcaacga gcgcaacccc tattgtcagt 1140

agccagcagg taaagctggg cactctgatg agactgccag ggataacctg gaggaaggtg 1200

gggatgacgt caaatcatca tgcccccttat gatttgggct acacacgtgc tacaatggcg 1260

taaacaaaga gaagcgagcc tgcgaggggg agcaaatctc aaaaataacg tctcagttcg 1320

gattgtagtc tgcaactcga ctacatgaag ctggaatcgc tagtaatcgc agatcagaat 1380

gctgcggtga atacgttccc gggtcttgta cacaccgccc gtcacaccat gggagtcgga 1440

aatgcccgaa gccagtgacc caagcgaaag cagggagctg tcgaaggcag gtctgataac 1500

tggggtgaag tcgtaacaag gtagccgtat cggaaggtgc ggctggatca cctccttt 1558

<210> 13

<211> 1529

<212> DNA

<213> Flavonifractor_sp.

<400> 13

tattgagagt ttgatcctgg ctcaggatga acgctggcgg cgtgcttaac acatgcaagt 60

cgaacggagt gctcatgaca gaggattcgt ccaatggagt gagttactta gtggcggacg 120

ggtgagtaac gcgtgagtaa cctgccttgg agtggggaat aacaggtgga aacatctgct 180

aataccgcat gatgcagttg ggtcgcatgg ctctgactgc caaagattta tcgctctgag 240

atggactcgc gtctgattag ctggttggcg gggtaacggc ccaccaaggc gacgatcagt 300

agccggactg agaggttggc cggccacatt gggactgaga cacggcccag actcctacgg 360

gaggcagcag tggggaatat tgggcaatgg gcgcaagcct gacccagcaa cgccgcgtga 420

aggaagaagg ctttcgggtt gtaaacttct tttctcaggg acgaagcaag tgacggtacc 480

tgaggaataa gccacggcta actacgtgcc agcagccgcg gtaatacgta ggtggcgagc 540

gttatccgga tttactgggt gtaaagggcg tgtaggcggg actgcaagtc agatgtgaaa 600

accatgggct caacctgtgg cctgcatttg aaactgtagt tcttgagtac tggagaggca 660

gacggaattc ctagtgtagc ggtgaaatgc gtagatatta ggaggaacac cagtggcgaa 720

ggcggtctgc tggacagcaa ctgacgctga ggcgcgaaag cgtggggagc aaacaggatt 780

agataccctg gtagtccacg ctgtaaacga tggatactag gtgtgggggg tctgaccccc 840

tccgtgccgc agttaacaca ataagtatcc cacctgggga gtacgatcgc aaggttgaaa 900

ctcaaaggaa ttgacggggg cccgcacaag cggtggagta tgtggtttaa ttcgaagcaa 960

cgcgaagaac cttaccaggg cttgacatcc cggtgaccgg tgtagagata caccttcttc 1020

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tgtcctgggc cacacacgta ctacaatggt ggtcaacaga gggaagcaag accgcgaggt 1260

ggagcaaacc cctaaaagcc atcccagttc ggattgcagg ctgcaactcg cctgtatgaa 1320

gttggaatcg ctagtaatcg cggatcagca tgccgcggtg aatacgttcc cgggccttgt 1380

acacaccgcc cgtcacacca tgagagtcgg gaacacccga agtccgtagc ctaaccgcaa 1440

ggggggcgcg gccgaaggtg ggttcgataa ttggggtgaa gtcgtaacaa ggtagccgta 1500

tcggaaggtg cggctggatc acctccttt 1529

<210> 14

<211> 1514

<212> DNA

<213> Emergencia_timonensis

<400> 14

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gagcgagaag ccattgaccg atacttcggt aaagggatat ggcggaaagc ggcggacggg 120

tgagtaacgc gtaggcaacc tgccccttac agagggatag ccattggaaa cgatgattaa 180

gacctcataa cgcctccctc ccacatgagg gggaggccaa agattcatcg gtaagggatg 240

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cgacctgaga gggtgatcgg ccacattgga actgagacac ggtccaaact cctacgggag 360

gcagcagtgg ggaatattgc acaatgggcg gaagcctgat gcagcaacgc cgcgtgaggg 420

atgaaggcct tcgggtcgta aacctctgtc cttggggaag aaacaaatga cggtacccat 480

ggaggaagcc ccggctaact acgtgccagc agccgcggta atacgtaggg ggcgagcgtt 540

atccggaatt attgggcgta aagagtgcgt aggtggttac ctaagcgcag ggtctaaggc 600

aatggctcaa ccattgttcg ccctgcgaac tgggctactt gagtgcagga gaggaaagcg 660

gaattcctag tgtagcggtg aaatgcgtag atattaggag gaacaccagt ggcgaaggcg 720

gctttctgga ctgttactga cactgaggca cgaaagcgtg gggagcaaac aggattagat 780

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aggaattgac ggggacccgc acaagcagcg gagcatgtgg tttaattcga agcaacgcga 960

agaaccttac caggacttga catccccctg acagatcctt aaccggatcc ttcttcggac 1020

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ccgcaacgag cgcaaccctt gccattagtt gccatcattc agttgggcac tctaatggga 1140

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aaatcccaaa aaccggtccc agttcggact gcaggctgca acccgcctgc acgaagccgg 1320

agttgctagt aatcgtggat cagaatgcca cggtgaatgc gttcccgggt cttgtacaca 1380

ccgcccgtca caccatggaa gttgggggtg cccgaagccg gcagggagat atgctgtcta 1440

aggcaaaacc aatgactggg gtgaagtcgt aacaaggtag ccgtatcgga aggtgcggct 1500

ggatcacctc cttt 1514

<210> 15

<211> 1527

<212> DNA

<213> Clostridium_sp.

<400> 15

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aacgaggtaa atgagatgaa gttttcggat ggattcttat ttaccgagtg gcggacgggt 120

gagtaacgcg tgggtaacct gcctcataca gggggataac gattggaaac gattgctaat 180

accgcataag cgcacagtac cacatggtac agtgtgaaaa actccggtgg tatgagatgg 240

acccgcgtct gattagctag ttggtgaggt aacggcccac caaggcaacg atcagtagcc 300

gacctgagag ggtgaccggc cacattggga ctgagacacg gcccagactc ctacgggagg 360

cagcagtggg ggatattgca caatggagga aactctgatg cagcgacgcc gcgtgagtga 420

agaagtattt cggtatgtaa agctctatca gcagggaaga aaatgacggt acctgactaa 480

gaagccccgg ctaactacgt gccagcagcc gcggtaatac gtaggggca agcgttatcc 540

ggatttactg ggtgtaaagg gagcgtagac ggcgatgcaa gtctgaagtg aaatacccgg 600

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ttcctagtgt agcggtgaaa tgcgtagata ttaggaagaa caccagtggc gaaggcggct 720

tactggacag taactgacgt tcaggctcga aagcgtgggg agcaaacagg attagatacc 780

ctggtagtcc acgccgtaaa cgatgaatac taggtgtcgg gggacaaagt ctttcggtgc 840

cgccgcaaac gcaataagta ttccacctgg ggagtacgtt cgcaagaatg aaactcaaag 900

gaattgacgg ggacccgcac aagcggtgga gcatgtggtt taattcgaag caacgcgaag 960

aaccttacca aatcttgaca tccctctgaa aagcctttaa tcgggctcct ccttcgggac 1020

agaggtgaca ggtggtgcat ggttgtcgtc agctcgtgtc gtgagatgtt gggttaagtc 1080

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atttgggcta cacacgtgct acaatggcgt aaacaaagag aggcgaagct gtgaggcaga 1260

gcaaatctca aaaataacgt ctcagttcgg attgtagtct gcaactcgac tacatgaagc 1320

tggaatcgct agtaatcgcg gatcagaatg ccgcggtgaa tacgttcccg ggtcttgtac 1380

acaccgcccg tcacaccatg ggagtcggaa atgcccgaag ccagtgaccc aagcgaaagc 1440

agggagctgt cgaaggcagg tctgataact ggggtgaagt cgtaacaagg tagccgtatc 1500

ggaaggtgcg gctggatcac ctccttt 1527

<210> 16

<211> 986

<212> DNA

<213> Clostridium_sp.

<220><221> misc_feature

<222> (1)

<223> n is a, c, g, or t

<400> 16

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agggctcaac cctcaaactg ccattgaaac tgtggttctt gagtgaagta gaggtaggcg 120

gaattcccgg tgtagcggtg gaatgcgtag agatcgggag gaacaccagt ggcgaaggcg 180

gcctactggg ctttaactga cgctgaggca cgaaagcatg ggtagcaaac aggattagat 240

accctggtag tccatgccgt aaacgatgat tactaggtgt ggggggtctg acccccteeg 300

tgccggagtt aacacaataa gtaatccacc tggggagtac ggccgcaagg ttgaaactca 360

aaggaattga cgggggcccg cacaagcagt ggagtatgtg gtttaattcg acgcaacgcg 420

aagaacctta ccaggtcttg acatccaact aacgaggtag agatacgtca ggtgcccttc 480

ggggaaagtt gagacaggtg gtgcatggtt gtcgtcagct cgtgtcgtga gatgttgggt 540

taagtcccgc aacgagcgca acccttgtga ttagttgcta cgcaagagca ctctaatcag 600

actgccgttg acaaaacgga ggaaggtggg gatgacgtca aatcatcatg ccctttatga 660

cctgggctac acacgtacta caatggccgt aaacagagag aggcgacacc gcgaggtgaa 720

gcgaaaccct aaaaacggtc tcagttcgga ttgtaggctg caacccgcct acatgaagtt 780

ggaattgcta gtaatcgcgg atcagcatgc cgcggtgaat acgttcccgg gccttgtaca 840

caccgcccgt cacaccatgg gagccggtaa tacccgaagt cagtagtcta accgcaaggg 900

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gaaggtgcgg ctggatcacc tccttt 986

<210> 17

<211> 1081

<212> DNA

<213> Clostridium_sp.

<220><221> misc_feature

<222> (660)

<223> n is a, c, g, or t

<400> 17

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acgcagcaac gccgcgtgat tgaagaaggc cttcgggttg taaagatctt taattaggga 120

cgaaataaat gacggtacct gaagaataag ctccggctaa ctacgtgcca gcagccgcgg 180

taatacgtag ggagcaagcg ttatccggat ttactgggtg taaagggcgc gcaggcgggc 240

cggtaagttg gaagtgaaat ctatgggctt aacccataaa ctgctttcaa aactgctggt 300

cttgagtgat ggagaggcag gcggaattcc gtgtgtagcg gtgaaatgcg tagatatacg 360

gaggaacacc agtggcgaag gcggcctgct ggacattaac tgacgctgag gcgcgaaagc 420

gtggggagca aacaggatta gataccctgg tagtccacgc cgtaaacgat ggatactagg 480

tgtgggaggt attgacccct tccgtgccgc agttaacaca ataagtatcc cacctgggga 540

gtacggccgc aaggttgaaa ctcaaaggaa ttgacggggg cccgcacaag cagtggagta 600

tgtggtttaa ttcgaagcaa cgcgaagaac cttaccaggt cttgacatcc cgatgaccgn 660

cttttcttcg gaacatcggt gacaggtggt gcatggttgt cgtcagctcg tgtcgtgaga 720

tgttgggtta agtcccgcaa cgagcgcaac ccttacggtt agttgatacg caagatcact 780

ctagccggac tgccgttgac aaaacggagg aaggtgggga cgacgtcaaa tcatcatgcc 840

ccttatgacc tgggctacac acgtactaca atggcagtca tacagaggga agcaaaaccg 900

cgaggtggag caaatcccta aaagctgtcc cagttcagat tgcaggctgc aacccgcctg 960

catgaagtcg gaattgctag taatcgcgga tcagcatgcc gcggtgaata cgttcccggg 1020

ccttgtacac accgcccgtc acaccatgag agccgtcaat acccgaagtc cgtagcctaa 1080

c 1081

<210> 18

<211> 1526

<212> DNA

<213> Clostridium_sp.

<400> 18

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cgaacggggt tattttggaa atctcttcgg agatggaatt cttaacctag tggcggacgg 120

gtgagtaacg cgtgagcaat ctgcctttag gagggggata acagtcggaa acggctgcta 180

ataccgcata atacgtttgg gaggcatctc ttgaacgtca aagattttat cgcctttaga 240

tgagctcgcg tctgattagc tggttggcgg ggtaacggcc caccaaggcg acgatcagta 300

gccggactga gaggttgaac ggccacattg ggactgagac acggcccaga ctcctacggg 360

aggcagcagt ggggaatatt gcgcaatggg ggaaaccctg acgcagcaac gccgcgtgat 420

tgaagaaggc cttcgggttg taaagatctt taatcaggga cgaaaaatga cggtacctga 480

agaataagct ccggctaact acgtgccagc agccgcggta atacgtaggg agcaagcgtt 540

atccggattt actgggtgta aagggcgcgc aggcgggccg gcaagttggg agtgaaatcc 600

cggggcttaa ccccggaact gctttcaaaa ctgctggtct tgagtgatgg agaggcaggc 660

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taccctggta gtccacgccg taaacgatgg atactaggtg tgggaggtat tgacccctc 840

cgtgccgcag ttaacacaat aagtatccca cctggggagt acggccgcaa ggttgaaact 900

caaaggaatt gacgggggcc cgcacaagca gtggagtatg tggtttaatt cgaagcaacg 960

cgaagaacct taccaggtct tgacatcccg atgaccggcg tagagatacg ccctctcttc 1020

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ctgggctaca cacgtactac aatggcagtc atacagaggg aagcaatacc gcgaggtgga 1260

gcaaatccct aaaagctgtc ccagttcaga ttgcaggctg caacccgcct gcatgaagtc 1320

ggaattgcta gtaatcgcgg atcagcatgc cgcggtgaat acgttcccgg gccttgtaca 1380

caccgcccgt cacaccatga gagccgtcaa tacccgaagt ccgtagccta accgcaaggg 1440

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gaaggtgcgg ctggatcacc tccttt 1526

<210> 19

<211> 1529

<212> DNA

<213> Flavonifractor_sp.

<400> 19

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<211> 1529

<212> DNA

<213> Intestinimonas_massiliensis

<400> 20

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<211> 1522

<212> DNA

<213> Clostridium_sp.

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<210> 22

<211> 1512

<212> DNA

<213> Blautia_faecis

<220><221> misc_feature

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<400> 22

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<210> 23

<211> 1513

<212> DNA

<213> Clostridium_disporicum

<400> 23

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<211> 1511

<212> DNA

<213> Anaerostipes_sp.

<400> 24

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<210> 25

<211> 1513

<212> DNA

<213> Ruminococcus_bicirculans

<400> 25

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<211> 1511

<212> DNA

<213> Ruminococcus_bicirculans

<400> 26

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<210> 27

<211> 1553

<212> DNA

<213> Streptococcus gordonii

<400> 27

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<211> 1553

<212> DNA

<213> Streptococcus gordonii

<400> 28

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<210> 29

<211> 1553

<212> DNA

<213> Streptococcus gordonii

<400> 29

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<211> 1553

<212> DNA

<213> Streptococcus gordonii

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<211> 1509

<212> DNA

<213> Akkermansia_muciniphila

<400> 31

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<400> 33

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<211> 1529

<212> DNA

<213> Eubacterium rectale

<400> 34

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<210> 36

<211> 1529

<212> DNA

<213> Eubacterium rectale

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<212> DNA

<213> Eubacterium rectale

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<210> 39

<211> 1506

<212> DNA

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<211> 1506

<212> DNA

<213> Eggerthella_lenta

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<212> DNA

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<211> 1529

<212> DNA

<213> Eubacterium eligens

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<211> 1530

<212> DNA

<213> Eubacterium eligens

<400> 44

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tcaaaggaat tgacggggac ccgcacaagc ggtggagcat gtggtttaat tcgaagcaac 960

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tgtacacacc gcccgtcaca ccatgggagt cgaaaatgcc cgaagtcggt gacctaacgt 1440

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atcggaaggt gcggctggat cacctccttt 1530

<210> 45

<211> 1529

<212> DNA

<213> Eubacterium eligens

<400> 45

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cgggtgagta acgcgtgggt aacctgcctt gtactggggg atagcagctg gaaacggctg 180

gtaataccgc ataagcgcac aatgttgcat gacatagtgt gaaaaactcc ggtggtataa 240

gatggacccg cgtctgatta gctagttggt gagataacag cccaccaagg cgacgatcag 300

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ggaggcagca gtggggaata ttgcacaatg gaggaaactc tgatgcagcg acgccgcgtg 420

agtgaagaag taattcgtta tgtaaagctc tatcagcagg gaagatagtg acggtacctg 480

actaagaagc tccggctaaa tacgtgccag cagccgcggt aatacgtatg gagcaagcgt 540

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cggctcactg gactgtaact gacactgagg ctcgaaagcg tggggagcaa acaggattag 780

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tcggaaggtg cggctggatc acctccttt 1529

<210> 46

<211> 1529

<212> DNA

<213> Eubacterium eligens

<400> 46

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cgggtgagta acgcgtgggt aacctgcctt gtactggggg atagcagctg gaaacggctg 180

gtaataccgc ataagcgcac aatgttgcat gacatggtgt gaaaaactcc ggtggtataa 240

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agtgaagaag taattcgtta tgtaaagctc tatcagcagg gaagatagtg acggtacctg 480

actaagaagc tccggctaaa tacgtgccag cagccgcggt aatacgtatg gagcaagcgt 540

tatccggatt tactgggtgt aaagggagtg taggtggcca tgcaagtcag aagtgaaaat 600

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tggaattcct agtgtagcgg tgaaatgcgt agatattagg aggaacacca gtggcgaagg 720

cggctcactg gactgtaact gacactgagg ctcgaaagcg tggggagcaa acaggattag 780

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gtacacaccg cccgtcacac catgggagtc gaaaatgccc gaagtcggtg acctaacgca 1440

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tcggaaggtg cggctggatc acctccttt 1529

<210> 47

<211> 1529

<212> DNA

<213> Eubacterium eligens

<400> 47

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cgaacgaagc atttgcgaca gatttttcg gaatgaagtt gcttatgact gagtggcgga 120

cgggtgagta acgcgtgggt aacctgcctt gtactggggg atagcagctg gaaacggctg 180

gtaataccgc ataagcgcac aatgttgcat gacatggtgt gaaaaactcc ggtggtataa 240

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agtgaagaag taattcgtta tgtaaagctc tatcagcagg gaagatagtg acggtacctg 480

actaagaagc tccggctaaa tacgtgccag cagccgcggt aatacgtatg gagcaagcgt 540

tatccggatt tactgggtgt aaagggagtg taggtggcca tgcaagtcag aagtgaaaat 600

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tggaattcct agtgtagcgg tgaaatgcgt agatattagg aggaacacca gtggcgaagg 720

cggctcactg gactgtaact gacactgagg ctcgaaagcg tggggagcaa acaggattag 780

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tcggaaggtg cggctggatc acctccttt 1529

<210> 48

<211> 1531

<212> DNA

<213> Eubacterium ventriosum

<400> 48

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gaacgaagca ccttggacag aatccttcgg gaggaagacc attgtgactg agtggcggac 120

gggtgagtaa cgcgtgggta acctgccttg tacaggggga taacagttgg aaacgactgc 180

taataccgca taagcgcaca gtaccgcatg gtacggtgtg aaaaactccg gtggtacaag 240

atggacccgc gtctgattag ctggttggtg aggtaacggc ccaccaaggc gacgatcagt 300

agccgacttg agagagtgat cggccacatt gggactgaga cacggcccaa actcctacgg 360

gaggcagcag tagggaatat tgcacaatgg gggaaaccct gatgcagcga cgccgcgtga 420

aggaagaagt atttcggtat gtaaacttct atcagcaagg aagaaaatga cggtacttga 480

ctaagaagcc ccggctaaat acgtgccagc agccgcggta atacgtatgg ggcaagcgtt 540

atccggattt actgggtgta aagggagcgt aggcggcatg gcaagtcaga agtgaaagcc 600

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ggcttactgg acgattactg acgctgaggc tcgaaagcgt ggggagcaaa caggattaga 780

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gtacacaccg cccgtcacac catgggagtt ggatatgccc gaagtcagtg acccaaccgt 1440

aaggagggag ctgccgaagg tggagccgat aactggggtg aagtcgtaac aaggtagccg 1500

tatcggaagg tgcggctgga tcacctcctt t 1531

<210> 49

<211> 1527

<212> DNA

<213> Ruminococcus obeum

<400> 49

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gaacgggaaa cttttcattg aagcttcggc agatttggtc tgtttctagt ggcggacggg 120

tgagtaacgc gtgggtaacc tgccttatac agggggataa caaccagaaa tggttgctaa 180

taccgcataa gcgcacagga ccgcatggtc cggtgtgaaa aactccggtg gtataagatg 240

gacccgcgtt ggattagcta gttggcaggg taacggccta ccaaggcgac gatccatagc 300

cggcctgaga gggtgaacgg ccacattggg actgagacac ggcccagact cctacgggag 360

gcagcagtgg ggaatattgc acaatggggg aaaccctgat gcagcgacgc cgcgtgaagg 420

aagaagtatc tcggtatgta aacttctatc agcagggaag atagtgacgg tacctgacta 480

agaagccccg gctaactacg tgccagcagc cgcggtaata cgtaggggggc aagcgttatc 540

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ggaaggtgcg gctggatcac ctccttt 1527

<210> 50

<211> 1527

<212> DNA

<213> Ruminococcus obeum

<400> 50

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gaacgggaaa cttttcattg aagcttcggc agatttggtc tgtttctagt ggcggacggg 120

tgagtaacgc gtgggtaacc tgccttatac agggggataa caaccagaaa tggttgctaa 180

taccgcataa gcgcacagga ccgcatggtc tagtgtgaaa aactccggtg gtataagatg 240

gacccgcgtt ggattagcta gttggcaggg taacggccta ccaaggcgac gatccatagc 300

cggcctgaga gggtgaacgg ccacattggg actgagacac ggcccagact cctacgggag 360

gcagcagtgg ggaatattgc acaatggggg aaaccctgat gcagcgacgc cgcgtgaagg 420

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agaagccccg gctaactacg tgccagcagc cgcggtaata cgtaggggggc aagcgttatc 540

cggatttact gggtgtaaag ggagcgtaga cggactggca agtctgatgt gaaaggcggg 600

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ggaaggtgcg gctggatcac ctccttt 1527

<210> 51

<211> 1100

<212> DNA

<213> Ruminococcus obeum

<400> 51

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ctgatgcagc gacgccgcgt gaaggaagaa gtatctcggt atgtaaactt ctatcagcag 120

ggaagatagt gacggtacct gactaagaag ccccggctaa ctacgtgcca gcagccgcgg 180

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<210> 52

<211> 984

<212> DNA

<213> Ruminococcus obeum

<400> 52

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accttaccaa gtctgacatc ccct 984

<210> 53

<211> 939

<212> DNA

<213> Ruminococcus obeum

<400> 53

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taccgcataa gcgcacagga ccgcatggtc cggtgtgaaa aactccggtg gtataagatg 240

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cggcctgaga gggtgaacgg ccacattggg actgagacac ggcccagact cctacgggag 360

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agaagccccg gctaactacg tgccagcagc cgcggtaata cgtaggggcc aagcgttatc 540

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<210> 54

<211> 1529

<212> DNA

<213> Ruminococcus torques

<400> 54

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<210> 55

<211> 1529

<212> DNA

<213> Ruminococcus torques

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<210> 56

<211> 1056

<212> DNA

<213> Ruminococcus torques

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gggctcaacc ccgggactgc attggaaact gttcatctag agtgctggag aggtaagtgg 660

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cttactggac agtaactgac gttgaggctc gaaagcgtgg ggagcaaaca ggattagata 780

ccctggtagt ccacgccgta aacgatgact actaggtgtc gggtggcaaa gccattcggt 840

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<210> 57

<211> 1529

<212> DNA

<213> Ruminococcus torques

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<210> 58

<211> 1177

<212> DNA

<213> Ruminococcus torques

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ccctggtagt ccacgccgta aacgatgact actaggtgtc gggtggcaaa gccattcggt 840

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<210> 59

<211> 1528

<212> DNA

<213> Ruminococcus torques

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<210> 63

<211> 857

<212> DNA

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<211> 1442

<212> DNA

<213> Anaerostipes_caccae

<220><221> misc_feature

<222> (1442)

<223> n is a, c, g, or t

<400> 64

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ggtgagtaac gcgtggggaa cctgccctat acagggggat aacagctgga aacggctgct 180

aataccgcat aagcgcacag aatcgcatga ttcagtgtga aaagccctgg cagtatagga 240

tggtcccgcg tctgattagc tggttggtga ggtaacggct caccaaggcg acgatcagta 300

gccggcttga gagagtgaac ggccacattg ggactgagac acggcccaaa ctcctacggg 360

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ctaagaagcc ccggctaact acgtgccagc agccgcggta atacgtaggg ggcaagcgtt 540

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agctggaatc gctagtaatc gtgaatcaga atgtcacggt gaatacgttc ccgggtcttg 1380

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an 1442

<210> 65

<211> 1530

<212> DNA

<213> Anaerostipes_caccae

<400> 65

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ggtgagtaac gcgtggggaa cctgccctat acaggggat aacagctgga aacggctgct 180

aataccgcat aagcgcacag aatcgcatga ttcagtgtga aaagccctgg cagtatagga 240

tggtcccgcg tctgattagc tggttggtga ggtaacggct caccaaggcg acgatcagta 300

gccggcttga gagagtgaac ggccacattg ggactgagac acggcccaaa ctcctacggg 360

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ctaagaagcc ccggctaact acgtgccagc agccgcggta atacgtaggg ggcaagcgtt 540

atccggaatt actgggtgta aagggtgcgt aggtggcatg gtaagtcaga agtgaaagcc 600

cggggcttaa ccccgggact gcttttgaaa ctgtcatgct ggagtgcagg agaggtaagc 660

ggaattccta gtgtagcggt gaaatgcgta gatattagga ggaacaccag tggcgaaggc 720

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gaagcaaatc ccagaaataa cgtctcagtt cggattgtag tctgcaactc gactacatga 1320

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tacacaccgc ccgtcacacc atgggagtca gtaacgcccg aagtcagtga cccaaccgca 1440

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atcggaaggt gcggctggat cacctccttt 1530

<210> 66

<211> 1531

<212> DNA

<213> Anaerostipes_caccae

<400> 66

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ggtgagtaac gcgtggggaa cctgccctat acagggggga taacagctgg aaacggctgc 180

taataccgca taagcgcaca gaatcgcatg attcagtgtg aaaagccctg gcagtatagg 240

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agccggcttg agagagtgaa cggccacatt gggactgaga cacggcccaa actcctacgg 360

gaggcagcag tggggaatat tgcacaatgg gggaaaccct gatgcagcga cgccgcgtga 420

gtgaagaagt atttcggtat gtaaagctct atcagcaggg aagaaaacag acggtacctg 480

actaagaagc cccggctaac tacgtgccag cagccgcggt aatacgtagg gggcaagcgt 540

tatccggaat tactgggtgt aaagggtgcg taggtggcat ggtaagtcag aagtgaaagc 600

ccggggctta accccgggac tgcttttgaa actgtcatgc tggagtgcag gagaggtaag 660

cggaattcct agtgtagcgg tgaaatgcgt agatattagg aggaacacca gtggcgaagg 720

cggcttactg gactgtcact gacactgatg cacgaaagcg tggggagcaa acaggattag 780

ataccctggt agtccacgcc gtaaacgatg aatactaggt gtcggggccg tagaggcttc 840

ggtgccgcag caaacgcagt aagtattcca cctggggagt acgttcgcaa gaatgaaact 900

caaaggaatt gacggggacc cgcacaagcg gtggagcatg tggtttaatt cgaagcaacg 960

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gtacacaccg cccgtcacac catgggagtc agtaacgccc gaagtcagtg acccaaccgc 1440

aaggagggag ctgccgaagg tgggaccgat aactggggtg aagtcgtaac aaggtagccg 1500

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<210> 67

<211> 1505

<212> DNA

<213> Eubacterium siraeum

<400> 67

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acctggctct aagaggggga caacagttgg aaacgactgc taataccgca taacgtatcg 180

ggatggcatc ttcctgatac caaagatttt atcgcttaga gatgggctcg cgtctgatta 240

gatagttggc ggggtaacgg cccaccaagt cgacgatcag tagccggact gagaggttga 300

acggccacat tgggactgag acacggccca gactcctacg ggaggcagca gtgggggata 360

ttggacaatg ggggcaaccc tgatccagcg acgccgcgtg agggaagaag gttttcggat 420

tgtaaacctc tgttgacgga gaaaaaaatg atggtatccg tttagaaagc cacggctaac 480

tacgtgccag cagccgcggt aatacgtagg tggcaagcgt tgtccggaat tactgggtgt 540

aaagggagtg taggcgggat atcaagtcag aagtgaaaat tacgggctca actcgtaacc 600

tgcttttgaa actgacattc ttgagtgaag tagaggcaag cggaattcct agtgtagcgg 660

tgaaatgcgt agatattagg aggaacacca gtggcgaagg cggcttgctg ggcttttact 720

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tgcatggttg tcgtcagctc gtgtcgtgag atgttgggtt aagtcccgca acgagcgcaa 1080

cccttatcat tagttgctac gcaagagcac tctaatgaga ctgccgttga caaaacggag 1140

gaaggtgggg atgacgtcaa atcatcatgc cctttatgac ctgggctaca cacgtactac 1200

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ccttt 1505

<210> 68

<211> 1505

<212> DNA

<213> Eubacterium siraeum

<400> 68

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acctggctct aagaggggga caacagttgg aaacgactgc taataccgca taacgtatcg 180

ggatggcatc ttcctgatac caaagatttt atcgcttaga gatgggctcg cgtctgatta 240

gatagttggc ggggtaacgg cccaccaagt cgacgatcag tagccggact gagaggttga 300

acggccacat tgggactgag acacggccca gactcctacg ggaggcagca gtgggggata 360

ttggacaatg ggggcaaccc tgatccagcg acgccgcgtg agggaagaag gttttcggat 420

tgtaaacctc tgttgacgga gaaaaaaatg atggtatccg tttagaaagc cacggctaac 480

tacgtgccag cagccgcggt aatacgtagg tggcaagcgt tgtccggaat tactgggtgt 540

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cccttatcat tagttgctac gcaagagcac tctaatgaga ctgccgttga caaaacggag 1140

gaaggtgggg atgacgtcaa atcatcatgc cctttatgac ctgggctaca cacgtactac 1200

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agttggcaac acccgaagtc ggtagtctaa ccgcaaggag gacgccgccg aaggtggggt 1440

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ccttt 1505

<210> 69

<211> 1505

<212> DNA

<213> Eubacterium siraeum

<400> 69

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acctggctct aagagggggа caacagttgg aaacgactgc taataccgca tgatgtatcg 180

ggatggcatc ttcctgatac caaagatttt atcgcttaga gatgggctcg cgtctgatta 240

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tacgtgccag cagccgcggt aatacgtagg tggcaagcgt tgtccggaat tactgggtgt 540

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tgaaatgcgt agatattagg aggaacacca gtggcgaagg cggcttgctg ggcttttact 720

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tgatgattag ggttaagtcg taacaaggta gccgtatcgg aaggtgcggc tggatcacct 1500

ccttt 1505

<210> 70

<211> 1505

<212> DNA

<213> Eubacterium siraeum

<400> 70

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acctggctct aagagggggga caacagttgg aaacgactgc taataccgca taacgtatcg 180

ggatggcatc ttcctgatac caaagatttt atcgcttaga gatgggctcg cgtctgatta 240

gatagttggc ggggtaacgg cccaccaagt cgacgatcag tagccggact gagaggttga 300

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ccttt 1505

<210> 71

<211> 1548

<212> DNA

<213> Clostridium leptum

<400> 71

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atttaactta gtggcggacg ggtgagtaac gcgtgagtaa cctgcctttc agagggggat 180

aacgttctga aaagaacgct aataccgcat aacatcaatt tatcgcatga taggttgatc 240

aaaggagcaa tccgctggaa gatggactcg cgtccgatta gccagttggc ggggtaacgg 300

cccaccaaag cgacgatcgg tagccggact gagaggttga acggccacat tgggactgag 360

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aggaacacca gtggcgaagg cggcctactg ggctttaact gacgctgaag cacgaaagca 780

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gccagtagtt caaccgcaag gagagcgctg tcgaaggtag gattggcgac tggggtgaag 1500

tcgtaacaag gtagccgtat cggaaggtgc ggctggatca cctccttt 1548

<210> 72

<211> 1548

<212> DNA

<213> Clostridium leptum

<400> 72

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atttaactta gtggcggacg ggtgagtaac gcgtgagtaa cctgcctttc agagggggat 180

aacgttctga aaagaacgct aataccgcat aacatcaatt tatcgcatga taggttgatc 240

aaaggagcaa tccgctggaa gatggactcg cgtccgatta gccagttggc ggggtaacgg 300

cccaccaaag cgacgatcgg tagccggact gagaggttga acggccacat tgggactgag 360

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<211> 1509

<212> DNA

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<212> DNA

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<210> 82

<211> 1169

<212> DNA

<213> Clostridium_bartlettii

<400> 82

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<210> 83

<211> 1501

<212> DNA

<213> Clostridium_bartlettii

<400> 83

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<210> 84

<211> 905

<212> DNA

<213> Clostridium_bartlettii

<400> 84

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<210> 85

<211> 1501

<212> DNA

<213> Clostridium_bartlettii

<400> 85

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t 1501

<210> 86

<211> 1524

<212> DNA

<213> Clostridium ramosum

<400> 86

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<211> 1026

<212> DNA

<213> Clostridium scindens

<400> 87

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<210> 88

<211> 1532

<212> DNA

<213> Clostridium scindens

<400> 88

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<210> 89

<211> 1521

<212> DNA

<213> Anaerotruncus_colihominis

<400> 89

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<211> 1521

<212> DNA

<213> Anaerotruncus_colihominis

<400> 90

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<213> Anaerotruncus_colihominis

<400> 91

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<212> DNA

<213> Clostridium spiroforme

<400> 93

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gctacacacg tgctacaatg atggagcaga gggaagcgaa gccgcgagtg agcaaaccca 1260

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<211> 886

<212> DNA

<213> Clostridium spiroforme

<400> 94

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<212> DNA

<213> Clostridium spiroforme

<400> 95

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<212> DNA

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<210> 97

<211> 1517

<212> DNA

<213> Anaerofustis_stercorihominis

<400> 97

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<211> 1527

<212> DNA

<213> Clostridiales_bacterium_1_7_47FAA

<400> 98

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<212> DNA

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<210> 100

<211> 1076

<212> DNA

<213> Roseburia_intestinalis

<400> 100

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<211> 1296

<212> DNA

<213> Dorea_formicigenerans

<400> 118

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<211> 1527

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<400> 119

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<210> 120

<211> 1424

<212> DNA

<213> Eubacterium hallii

<400> 120

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<210> 121

<211> 1529

<212> DNA

<213> Ruminococcaceae_bacterium_D16

<400> 121

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<210> 122

<211> 1544

<212> DNA

<213> Streptococcus vestibularis

<400> 122

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<211> 1544

<212> DNA

<213> Streptococcus vestibularis

<400> 123

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<211> 1543

<212> DNA

<213> Streptococcus vestibularis

<400> 124

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<210> 125

<211> 1542

<212> DNA

<213> Streptococcus vestibularis

<400> 125

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<210> 126

<211> 1544

<212> DNA

<213> Streptococcus vestibularis

<400> 126

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<210> 127

<211> 1544

<212> DNA

<213> Streptococcus vestibularis

<400> 127

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<211> 1544

<212> DNA

<213> Streptococcus thermophilus

<400> 128

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 129

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<210> 130

<211> 1544

<212> DNA

<213> Streptococcus thermophilus

<400> 130

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 131

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 132

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<212> DNA

<213> Prevotella buccae

<400> 133

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<210> 134

<211> 1529

<212> DNA

<213> Lachnospiraceae_bacterium_5_1_63FAA

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<210> 135

<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_8_1_57FAA

<400> 135

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<210> 136

<211> 1545

<212> DNA

<213> Streptococcus_australis

<400> 136

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<210> 137

<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_4_1_37FAA

<400> 137

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gatgaagtat ttcggtatgt aaacttctat cagcagggaa gaaaatgacg gtacctgact 480

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aggaattgac ggggacccgc acaagcggtg gagcatgtgg tttaattcga agcaacgcga 960

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tcccgcaacg agcgcaaccc ctatcttcag tagccagcgg taaggccggg cactctggag 1140

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cggaaggtgc ggctggatca cctccttt 1528

<210> 138

<211> 1544

<212> DNA

<213> Streptococcus sanguis

<400> 138

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<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_3_1_46FAA

<400> 139

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<210> 140

<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_6_1_63FAA

<400> 140

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<213> Lachnospiraceae_bacterium_9_1_43BFAA

<400> 141

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<210> 142

<211> 1312

<212> DNA

<213> Ruminococcus bromii

<400> 142

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<211> 976

<212> DNA

<213> Coprococcus_catus

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<400> 143

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gtgaaatgcg tagatattag gaggaacacc agtggcgaag gcggcttact ggactgacaa 720

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cgtaaacgat gaatactagg tgtcgggggc tcataagagc tttcggtgcc gcagcaaacg 840

caataagtat tccacctggg gagtacgttc gcaagaatga aactcaaagg aattgacggg 900

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<210> 144

<211> 1522

<212> DNA

<213> Dysgonomonas_mossii

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cgggttgtaa acttcttttg tacaggaata aaagacatta cgtgtagtgt attgcatgta 480

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<210> 145

<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_1_4_56FAA

<400> 145

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<210> 146

<211> 1527

<212> DNA

<213> Lachnospiraceae_bacterium_3_1_57FAA_CT1

<400> 146

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agtaacgcgt gggaaacctg ccctgtaccg ggggataaca cttagaaata ggtgctaata 180

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<210> 147

<211> 1527

<212> DNA

<213> Lachnospiraceae_bacterium_3_1_57FAA_CT1

<400> 147

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agtaacgcgt gggaaacctg ccctgtaccg ggggataaca cttagaaata ggtgctaata 180

ccgcataagc gcacagcttc acatgaagca gtgtgaaaaa ctccggtggt acaggatggt 240

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<210> 148

<211> 1527

<212> DNA

<213> Lachnospiraceae_bacterium_3_1_57FAA_CT1

<400> 148

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agtaacgcgt gggaaacctg ccctgtaccg ggggataaca cttagaaata ggtgctaata 180

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gaagtatttc ggtatgtaaa gctctatcag cagggaagaa aatgacggta cctgactaag 480

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<210> 149

<211> 1532

<212> DNA

<213> Lachnospiraceae_bacterium_5_1_57FAA

<400> 149

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gtatcggaag gtgcggctgg atcacctcct tt 1532

<210> 150

<211> 1528

<212> DNA

<213> Lachnospiraceae_bacterium_1_1_57FAA

<400> 150

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<210> 151

<211> 1529

<212> DNA

<213> Lachnospiraceae_bacterium_2_1_58FAA

<400> 151

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<210> 152

<211> 1528

<212> DNA

<213> Roseburia_hominis

<400> 152

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<223> n is a, c, g, or t

<400> 160

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<400> 182

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ttgtacacac cgcccgtcaa gccatgaaag ccgggggtac ctgaagtgcg taaccgcaag 1440

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aggtgcggct ggaacacctc ctt 1523

<210> 196

<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 196

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acgtatccaa cctgccgatg actcggggat agcctttcga aagaaagatt aatacccgat 180

ggcatagttc ttccgcatgg tggaactatt aaagaatttc ggtcatcgat ggggatgcgt 240

tccattaggt tgttggcggg gtaacggccc accaagcctt cgatggatag gggttctgag 300

aggaaggtcc cccacattgg aactgagaca cggtccaaac tcctacggga ggcagcagtg 360

aggaatattg gtcaatggac gagagtctga accagccaag tagcgtgaag gatgactgcc 420

ctatgggttg taaacttctt ttatacggga ataaagtgag gcacgtgtgc ctttttgtat 480

gtaccgtatg aataaggatc ggctaactcc gtgccagcag ccgcggtaat acggaggatc 540

cgagcgttat ccggatttat tgggtttaaa gggagcgtag gcggacgctt aagtcagttg 600

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<210> 197

<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 197

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acgtatccaa cctgccgatg actcggggat agcctttcga aagaaagatt aatacccgat 180

ggcatagttc ttccgcatgg tagaactatt aaagaatttc ggtcatcgat ggggatgcgt 240

tccattaggt tgttggcggg gtaacggccc accaagcctt cgatggatag gggttctgag 300

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ctatgggttg taaacttctt ttatacggga ataaagtgag gcacgtgtgc ctttttgtat 480

gtaccgtatg aataaggatc ggctaactcc gtgccagcag ccgcggtaat acggaggatc 540

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ggattagata ccctggtagt ccacacagta aacgatgaat actcgctgtt tgcgatatac 840

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cttacgtccg gggctacaca cgtgttacaa tgggggggtac agaaggcagc tacacggcga 1260

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aggtgcggct ggaacacctc ctt 1523

<210> 198

<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 198

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acgtatccaa cctgccgatg actcggggat agcctttcga aagaaagatt aatacccgat 180

ggcatagttc ttccgcatgg tagaactatt aaagaatttc ggtcatcgat ggggatgcgt 240

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<210> 199

<211> 1051

<212> DNA

<213> Bacteroides vulgatus

<400> 199

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gatatacggc aagcggccaa gcgaaagcgt taagtattcc acctggggag tacgccggca 420

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tcgatgatac gcgaggaacc ttacccgggc ttaaattgca gatgaattac ggtgaaagcc 540

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ccgggccttg tacacaccgc ccgtcaagcc atgggagccg ggggtacctg aagtgcgtaa 960

ccgcgaggag cgccctaggg taaaactggt gactggggct aagtcgtaac aaggtagccg 1020

taccggaagg tgcggctgga acacctcctt t 1051

<210> 200

<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 200

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aaggtgcggc tggaacacct cctt 1524

<210> 201

<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 201

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<210> 202

<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 202

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<210> 203

<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 203

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<210> 204

<211> 1054

<212> DNA

<213> Bacteroides vulgatus

<400> 204

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<212> DNA

<213> Eubacterium_sp_3_1_31

<400> 205

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<210> 206

<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

<400> 206

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<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

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<210> 208

<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

<400> 208

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<210> 209

<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

<400> 209

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<210> 210

<211> 1544

<212> DNA

<213> Streptococcus salivarius

<400> 210

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<210> 211
<211> 1544
<212> DNA

<213> Streptococcus salivarius

<400> 211

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<210> 212
<211> 1544
<212> DNA

<213> Streptococcus salivarius
<400> 212

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<210> 213
<211> 1547
<212> DNA

<213> Streptococcus salivarius

<400> 213

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<210> 214

<211> 1544

<212> DNA

<213> Streptococcus salivarius

<400> 214

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<210> 215

<211> 1544

<212> DNA

<213> Streptococcus salivarius

<400> 215

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<210> 216
<211> 1544
<212> DNA

<213> Streptococcus salivarius
<400> 216

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<210> 217

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 217

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<210> 218
<211> 1521
<212> DNA

<213> Parabacteroides_distasonis
<400> 218

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<210> 219

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 219

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<210> 220

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 220

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<210> 221
<211> 1521
<212> DNA

<213> Parabacteroides_distasonis
<400> 221

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<211> 1531

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<213> Clostridiaceae_bacterium_JC118

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<211> 981

<212> DNA

<213> Anaerostipes_hadrus

<400> 223

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<211> 1537

<212> DNA

<213> Clostridium innocuum

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<211> 1537

<212> DNA

<213> Clostridium innocuum

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<211> 1537

<212> DNA

<213> Clostridium innocuum

<400> 226

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<212> DNA

<213> Clostridium innocuum

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aaagccgggg gtacctgaag tacgtaaccg caaggagcgt cctagggtaa aactggtaat 1080

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<211> 1137

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 240

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ctccgtgcca gcagccgcgg taatacggag gatccgagcg ttatccggat ttattgggtt 180

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<211> 1525

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 241

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atagtataat tagaccgcat ggtcttatta ttaaagaatt tcggttatcg atggggatgc 240

gttccattag gcagttggtg aggtaacggc tcaccaaacc ttcgatggat aggggttctg 300

agaggaaggt cccccacatt ggaactgaga cacggtccaa actcctacgg gaggcagcag 360

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ccctatgggt tgtaaacttc ttttatatgg gaataaagtt ttccacgtgt ggaattttgt 480

atgtaccata tgaataagga tcggctaact ccgtgccagc agccgcggta atacggagga 540

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tgtgaaagtt tgcggctcaa ccgtaaaatt gcagttgata ctggctgtct tgagtacagt 660

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<210> 242

<211> 1525

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 242

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atggtataat tagaccgcat ggtcttgtta ttaaagaatt tcggttatcg atggggatgc 240

gttccattag gcagttggtg aggtaacggc tcaccaaacc ttcgatggat aggggttctg 300

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<210> 243

<211> 1531

<212> DNA

<213> Sutterella_wadsworthensis

<400> 243

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ggaacgtgtc ttctagtggg ggataactgc ccgaaagggc agctaatacc gcatgagacc 180

tgagggtgaa agcgggggat cgcaagacct cgcgctggaa gagcggccga tgtccgatta 240

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<211> 921

<212> DNA

<213> Sutterella_wadsworthensis

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<222> (921)

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<400> 244

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<210> 245

<211> 1531

<212> DNA

<213> Sutterella_wadsworthensis

<400> 245

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<211> 1531

<212> DNA

<213> Sutterella_wadsworthensis

<400> 246

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<211> 1527

<212> DNA

<213> Clostridium_sp_KLE_1755

<400> 247

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<212> DNA

<213> Clostridium symbiosum

<400> 248

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<212> DNA

<213> Ruminococcus gnavus

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<211> 1530

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<213> Roseburia_faecis

<400> 259

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<400> 260

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<211> 1529

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<212> DNA

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<400> 263

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<400> 266

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<210> 267

<211> 1177

<212> DNA

<213> Ruminococcus obeum

<400> 267

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tacctgacta agaagccccg gctaactacg tgccagcagc cgcggtaata cgtagggggc 180

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<211> 1526

<212> DNA

<213> Blautia_sp.

<400> 268

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<210> 269

<211> 1526

<212> DNA

<213> Blautia_sp.

<400> 269

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taccgcataa gcgcacggta ccgcatggta cagtgtgaaa aactccggtg gtgtgagatg 240

gatccgcgtc tgattaggta gttggtgagg taacggccca ccaagccgac gatcagtagc 300

cgacctgaga gggtgaccgg ccacattggg actgagacac ggcccaaact cctacgggag 360

gcagcagtgg ggaatattgc acaatgggcg aaagcctgat gcagcaacgc cgcgtgagtg 420

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<210> 270

<211> 1530

<212> DNA

<213> Lachnospira pectinoschiza

<400> 270

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<210> 271

<211> 1226

<212> DNA

<213> Lactonifactor_longoviformis

<400> 271

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<210> 272

<211> 1530

<212> DNA

<213> Eubacterium contortum

<400> 272

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<211> 1530

<212> DNA

<213> Eubacterium contortum

<400> 273

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<211> 1530

<212> DNA

<213> Eubacterium contortum

<400> 274

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<211> 1530

<212> DNA

<213> Eubacterium contortum

<400> 275

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<210> 276

<211> 884

<212> DNA

<213> Eisenbergiella_tayi

<400> 276

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<212> DNA

<213> Ruminococcus_gnavus_sp

<400> 277

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<210> 278

<211> 1531

<212> DNA

<213> Clostridium_aldenense_sp

<400> 278

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<211> 1531

<212> DNA

<213> Clostridium_sp

<400> 279

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<211> 1529

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<213> Clostridium_lavalense

<400> 280

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<212> DNA

<213> Blautia_producta

<400> 281

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<400> 283

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<211> 1329

<212> DNA

<213> Streptococcus_infantis

<400> 284

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<213> Streptococcus_mitis_oralis_pneumoniae

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<211> 1539

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<212> DNA

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<400> 303

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<211> 1560

<212> DNA

<213> Veillonella dispar

<400> 304

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<210> 305

<211> 1560

<212> DNA

<213> Veillonella dispar

<400> 305

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<211> 1560

<212> DNA

<213> Veillonella dispar

<400> 306

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1560

<210> 307

<211> 1524

<212> DNA

<213> Rothia dentocariosa

<400> 307

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<211> 1524

<212> DNA

<213> Rothia dentocariosa

<400> 308

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<211> 1524

<212> DNA

<213> Rothia dentocariosa

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<211> 1560

<212> DNA

<213> Veillonella atypica

<400> 311

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<212> DNA

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 313

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<211> 1544

<212> DNA

<213> Streptococcus thermophilus

<400> 314

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 315

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<211> 1543

<212> DNA

<213> Streptococcus thermophilus

<400> 316

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<211> 1561

<212> DNA

<213> Lactobacillus animalis

<400> 317

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<211> 1548

<212> DNA

<213> Bilophila wadsworthia

<400> 318

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<212> DNA

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<212> DNA

<213> Bacteroides uniformis

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<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 341

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<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 342

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<211> 1523

<212> DNA

<213> Bacteroides uniformis

<400> 343

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<211> 1051

<212> DNA

<213> Bacteroides vulgatus

<400> 344

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<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 345

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<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 346

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<211> 1524

<212> DNA

<213> Bacteroides vulgatus

<400> 347

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<212> DNA

<213> Bacteroides vulgatus

<400> 348

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<211> 1054

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<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

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<211> 1535

<212> DNA

<213> Eubacterium_sp_3_1_31

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<212> DNA

<213> Eubacterium_sp_3_1_31

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<210> 355

<211> 1398

<212> DNA

<213> Morganella morganii

<400> 355

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ggctaactcc gtgccagcag ccgcggtaat acggagggtg caagcgttaa tcggaattac 420

tgggcgtaaa gcgcacgcag gcggttgatt gagtcagatg tgaaatcccc gggcttaacc 480

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<210> 356

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 356

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caacttacct atcagagggg gataacccgg cgaaagtcgg actaataccg catgaagcag 180

gggtcccgca tggggatatt tgctaaagat tcatcgctga tagataggca tgcgttccat 240

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tgcggctgga acacctcctt t 1521

<210> 357

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 357

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caacttgcct atcagagggg gataacccgg cgaaagtcgg actaataccg catgaagcag 180

gggccccgca tggggatatt tgctaaagat tcatcgctga tagataggca tgcgttccat 240

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gatcgtaaac ctcttttata agggaataaa gtgcgggacg tgtcctgttt tgtatgtacc 480

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<210> 358

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 358

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caacttacct atcagagggg gataacccgg cgaaagtcgg actaataccg catgaagcag 180

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tattggtcaa tgggcgcgag cctgaaccag ccaagtcgcg tgagggatga aggttctatg 420

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<210> 359

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 359

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caacttacct atcagagggg gataacccgg cgaaagtcgg actaataccg catgaagcag 180

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<210> 360

<211> 1521

<212> DNA

<213> Parabacteroides_distasonis

<400> 360

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tgcggctgga acacctcctt t 1521

<210> 361

<211> 1535

<212> DNA

<213> Citrobacter freundii

<400> 361

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ctcagactgg gataacatag ggaaacttat gctaataccg gataggtttt tggatcgcat 180

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tccgtaccgg aaggtgcgga tggatcacct ccttt 1535

<210> 362

<211> 1538

<212> DNA

<213> Citrobacter freundii

<400> 362

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tgaccagcca cactggaact gagacacggt ccagactcct acgggaggca gcagtgggga 360

atattgcaca atgggcgcaa gcctgatgca gccatgccgc gtgtatgaag aaggccttcg 420

ggttgtaaag tactttcagc gaggaggaag gcgttgtggt taataaccgc agcgattgac 480

gttactcgca gaagaagcac cggctaactc cgtgccagca gccgcggtaa tacggagggt 540

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ggcgaaggcg gccccctgga caaagactga cgctcaggtg cgaaagcgtg gggagcaaac 780

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<212> DNA

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<400> 369

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<213> Lactobacillus fermentum

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<211> 1572

<212> DNA

<213> Lactobacillus fermentum

<400> 371

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<211> 1572

<212> DNA

<213> Lactobacillus fermentum

<400> 372

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gatcacctcc tt 1572

<210> 373

<211> 1137

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 373

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gtgaaatgct tagatatcac gaagaactcc gattgcgaag gcagctcact ggactgcaac 360

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agtaaacgat gaatactcgc tgtttgcgat atacagtaag cggccaagcg aaagcattaa 480

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<210> 374

<211> 1137

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 374

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<210> 375

<211> 1525

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 375

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acacgtatcc aacctgccga taactcgggg atagcctttc gaaagaaaga ttaatacccg 180

atagtataat tagaccgcat ggtcttatta ttaaagaatt tcggttatcg atggggatgc 240

gttccattag gcagttggtg aggtaacggc tcaccaaacc ttcgatggat aggggttctg 300

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gaaggtgcgg ctggaacacc tcctt 1525

<210> 376

<211> 1525

<212> DNA

<213> Bacteroides thetaiotaomicron

<400> 376

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<210> 377

<211> 1569

<212> DNA

<213> Lactobacillus gasseri

<400> 377

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<210> 378

<211> 1566

<212> DNA

<213> Lactobacillus_casei_paracasei

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<212> DNA

<213> Lactobacillus_casei_paracasei

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<210> 386

<211> 1563

<212> DNA

<213> Lactobacillus plantarum

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<213> Enterobacter cloacae

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<212> DNA

<213> Escherichia coli

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<213> Escherichia coli

<400> 389

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<212> DNA

<213> Escherichia coli

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<210> 391

<211> 1538

<212> DNA

<213> Escherichia coli

<400> 391

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<210> 392

<211> 1538

<212> DNA

<213> Escherichia coli

<400> 392

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<212> DNA

<213> Escherichia coli

<400> 393

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<212> DNA

<213> Escherichia coli

<400> 394

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<212> DNA

<213> Klebsiella pneumoniae

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