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DEFECTIVE ENTITIES AND USES THEREFOR - AU2002357406

ABSTRACT & PATENT DETAILS

Inventor/s:
- **Cornford-Nairn, Renee**
- **Daggard, Grant Edward**
- **Mukkur, Trilochan Kanwaljit Singh**
- **Rossetti, Tony Robert**

Assignee/s:
- **Trilochan Kanwaljit Singh Mukkur**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) (19) World Intellectual Property Organization International Bureau (43) International Publication Date 24 July 2003 (24.07.2003) 0~ 1111111111111 11 11111111111111111111111111111111111 1111111111 11111111111111111111111111111111 (10) International Publication Number WO 03/060105 Al PCT (51) International Patent Classification 7 CI2N 1/20 (74) Agents: ARGAET, Victor, Peter et al.; Davies Collison Cave, Level 3, 303 Coronation Drive, Milton, Queensland (21) International Application Number: PCT/AU02/01768 4064 (AU). (22) International Filing Date: December 2002 (30.1 Filing Language: (26) Publication Language: (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, 2.2002) CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, IIR, IIU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, English LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, English SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW. Priority Data: PR 9776 28 December 2001 (28.12.2001) AU (71) Applicant (for all designated States except US): DELTA BIOTECHNOLOGY LIMITED [AU/AU]; McCullough Robertson, Level 12, Central Plaza 2, 66 Eagle Street, Brisbane, Queensland 4000 (AU). (72) Inventors; and Inventors/Applicants (for US only): CORN- FORD-NAIRN, Renee [AU/AU]; 74 Iron Bark Drive, Mt Rascal, Queensland 4350 DAGGARD, Grant, Edward [AU/AU]; 151 Long Street, Toowoomba, Queens- land 4350 MUKKUR, Trilochan, Kanwaljit, Singh [AU/AU]; 31 Ocean Street, Toowoomba, Queensland 4350 ROSSETTI, Tony, Robert [AU/AU]; Unit 3, 24 Lima Street, Auchenflower, Queensland 4066 (AU). (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG). Published: -with international search report -before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette. (54) Title: DEFECTIVE ENTITIES AND USES THEREFOR (57) Abstract: The present invention discloses the structure and sequence ofaroQ from Bordetella pertussis, which are useful inter alia for the production of the genetically modified attenuated Bordetella strains of the present invention and for detecting and isolating variant aroQ genes and expression products. The present invention also discloses attenuated Bordetella strains of pathogenic origin, and more particularly genetically modified Bordetella strains, which have been attenuated by disruption or inactivation of the aroQ gene. The genetically modified Bordetella strain of the present invention has a reduced capacity to propagate in a mammalian host, but remains viable in the host for a period of time sufficient to induce a protective immune response against the natural pathogenic Bordetella counterpart. The present invention is also directed to the use of such genetically modified Bordetella strains in immunopotentiating compositions for treating and/or preventing inter alia Bordetella infections, and particularly pathogenic infections, caused by Bordetella.

This page contains all relevant details related to patent number AU2002357406. This patent was filed on 30/12/2002 and has a status of GRANTED. The inventors associated with this patent are:

- Cornford-Nairn, Renee
- Daggard, Grant Edward

- Mukkur, Trilochan Kanwaljit Singh
- Rossetti, Tony Robert

The applicant/owner of the patent is registered as Trilochan Kanwaljit Singh Mukkur. They used the patent attorney firm Fisher Adams Kelly Pty Ltd to file this.

Australian patent AU2002357406 is one of over a million that we feature on IP in Australia which covers the entire spectrum of patents in Australia. Trilochan Kanwaljit Singh Mukkur is also one of thousands of applicants we've analysed. We also understand who are the most prolific inventors in Australia with details on all the patents attributed to individuals.

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PUBLICATIONS

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CLAIMS

CLAIMS 1. A genetically modified Bordetella strain having a partial or complete loss of 00 function in the endogenous aroQ gene and a lower capacity to propagate in a mammalian host but remaining viable in the host for a period of time sufficient to NO induce an immune response against a pathogenic Bordetella strain. 2. The genetically modified strain of claim 1, wherein the pathogenic Bordetella strain is a natural counterpart of the genetically modified Bordetella strain, or is a 0 10 related pathogenic Bordetella organism. 3. The genetically modified strain of claim 1, wherein the pathogenic strain is selected from Bordetella avium, Bordetella bronchiseptica, Bordetella holmesii, Bordetella parapertussis and Bordetella pertussis. 4. The genetically modified strain of claim 1, wherein the pathogenic Bordetella strain is Bordetella pertussis. The genetically modified strain of claim 1, comprising a disruption in the endogenous aroQ gene. 6. The genetically modified strain of claim 5, wherein the disruption has been introduced into the genome of a pathogenic strain of Bordetella by homologous recombination with a DNA targeting construct such that the targeting construct is stably integrated in the genome, wherein the disruption of the aroQ gene results in a reduced level and/or functional activity of the 3-dehydroquinase. 7. The genetically modified strain of claim 5, comprising an exogenous nucleic acid sequence in its genome, or on an extrachromosomal element, which is capable of abolishing or otherwise reducing the expression of aroQ or the level and/or functional activity of the 3-dehydroquinase encoded by aroQ.- 76- 00 8. The genetically modified strain of claim 5, comprising an exogenous nucleic N acid sequence in its

genome, or on an extrachromosomal element, which is capable of abolishing or otherwise reducing the expression of aroQ or the level and/or functional 00 activity of the 3-dehydroquinase encoded by aroQ, wherein the nucleic acid sequence comprises at lest a portion of aroQ, in the sense or anti-sense orientation, which is IND operably linked to a transcriptional control element. 9. The genetically modified strain of claim 1, further having a partial or complete C loss of function in at least one other endogenous gene selected from a purgene, 0 10 another aro gene, a pertussis toxin gene, or any other gene which contributes to survival in the host and/or to bacterial virulence, or a combination thereof. The genetically modified Bordetella strain of claim 1, comprising at least one exogenous gene which is capable for expressing an antigen that is heterologous or foreign to the Bordetella strain. 11. The genetically modified Bordetella strain of claim 10, wherein the heterologous or foreign antigen is derived from a pathogen that is unrelated to the Bordetella strain. 12. The genetically modified Bordetella strain of claim 10, wherein the heterologous or foreign antigen is derived from a pathogen that infects by the mucosal route. 13. An isolated polynucleotide comprising a nucleotide sequence set forth in SEQ ID NO: 1 or 3, or is complementary to the sequence set forth in SEQ ID NO: 1 or 3. 14. An isolated polynucleotide comprising a nucleotide sequence having at least sequence identity to at least a portion of the sequence set forth in SEQ ID NO: 1 or 3, wherein said portion is at least 150 nucleotides in length.-77- 00 The isolated polynucleotide of claim 14 wherein the nucleotide sequence has at least 90% sequence identity at least a portion of the sequence set forth in SEQ ID SNO: 1 or 3, wherein said portion is at least 150 nucleotides in length. 00 16. A nucleic acid construct for disrupting an aroQ gene in a Bordetella cell, N comprising: a) a non-homologous replacement portion; b) a first homology region located upstream of the non-homologous replacement portion, the first homology region having a nucleotide sequence with substantial identity to a first aroQ gene sequence; and c) a second homology region located downstream of the non- homologous replacement portion, the second homology region having a nucleotide sequence with substantial identity to a second aroQ gene sequence, the second aroQ gene sequence having a location downstream of the first aroQ gene sequence in a naturally occurring endogenous aroQ gene of the Bordetella cell. 17. The construct of claim 16, wherein the aroQ gene comprises the isolated polynucleotide as set forth in any one of claims 13 to 18. A vector comprising a nucleotide sequence that corresponds or is complementary to the isolated polynucleotide sequence as set forth in any one of claims 13 to 19. The vector of claim 18, wherein the vector is a DNA targeting vector. A host cell containing the construct of claim 16 or claim 17 or the vector of claim 18 or claim 19. 21. A method for producing a genetically modified Bordetella strain, comprising introducing the nucleic acid construct of claim 25 into a Bordetella cell under conditions such that the nucleic acid construct is homologously recombined into the aroQ gene in the genome of that cell to produce a genetically modified Bordetella cell containing a disrupted aroQ gene.-78- 00 22. The method of claim 21, wherein the genetically modified Bordetella cell containing the homologously recombined nucleic acid construct is further characterised by expressing reduced or undetectable levels of aroQ. 00 23. The method of claim 21, wherein the genetically modified Bordetella cell N lacks the ability to produce a functional 3-dehydroquinase encoded by said aroQ gene. 24. A composition, comprising the genetically modified Bordetella strain of claim C 10 1, together with a pharmaceutically acceptable carrier. The composition of claim 24, further comprising an adjuvant. 26. A composition of matter comprising dendritic cells which have been exposed to the genetically modified Bordetella strain of claim 1 for a time and under conditions sufficient to express a processed or modified antigen derived from the Bordetella strain for presentation to, and modulation of, T cells. 27. The composition of matter of claim 26, which is in the form of an in vitro cell culture. 28. A method for modulating an immune response, comprising administering to a patient in need of such treatment an effective amount of the genetically modified Bordetella strain of claim 1, or the composition of any one of claims 22-25 or the composition of matter of claim 26. 29. A method for the treatment and/or prophylaxis of whooping cough or related condition, comprising administering to a patient in need of such treatment an effective amount of the genetically modified Bordetella strain of claim 1, or the composition of any one of claims 22-25 or the composition of matter of claim 26.WO 03/060105 WO 03/60105PCT/A1J02/01768 1/8 BvgI (245) PvuII (306) EcoRi (396) SinaI (606) NgoMIV (671) EcoRl KlpnI (659) aroQ agrnent BssHI (874) FIGURE 1Z TdI7IDHj 099 Tog 009 3 6aa 3D 2*65vl me 465bz htm~~~~qS0 wnb vf3b'e jf1e06frat ona tm BES l i e &Z-6 Tslbv-z6 w o 14e62.ej 2.azi II.6CDI-{ n o~j 0;low :;)3Be -4a~ b4f6W.(I m :X 0051P 3~m z4.$mn 4 nnb& ie6bqb' DLLW DZ.. NZ.. Tot :uebG~u One 6d,) onefinodv Qumfied cuebdo .u bdz wuasjdod aucbanad avuEpdo euebqnode eufou anc6;in.d auabdo *ueBanode, ZNZO tmgBOu ausbd= cuchnndv numbe~jsd 21430 Oaf P 6 .0 :m:>Dvnmb~ 6=16.P m NIPUr rn

ISM..h aawnebn eto r~A2f5 oawnbaB;1411 Irlvr"4 B~~~~eu6f T.2 wn W B ~b SC 00 swBnah *fab'ebb veuOee0 ohea b 4090e 0D, 6 11-. f: z4 14;T Ba'~.4 *2M a Oaunb fp 6 6-ba OCTTO Dt 21435 auebont cafmbads a, 4.3 V a090 =0 07. WJ...D.O 404V.- Os 0 S1W S9LIOIZOfVIIJ 0191f A S01090/0 OAALWO 03/060105 WO 03/60105PCT/A1102/01768 3/8 p 998 193 pUSQBord8 S Highlighted insert ligated into pRTP 1 (a s BIS Hl pUSQBord9 898193 Mi Triple Ligation: Inserts from pUSQBord9 and pUSQBordl ligated together and inserted into pRTPl in the same reaction Ea.ndad 11-1s JgOM V Hindlil f9ll BaMI-Il PUSQBard1O ,Final Canetuact FIGURE 3WO 03/060105 WO 03/60105PCT/AU02/01768 4/8 1 23 45 6 2332 bD 2027 bp Inactivated gene size 1 approximately 1150 bp 564 bp 2000 bp 1200 bp aw 800 bp AroQ gene size approximately 500 bp FIGURE 4WO 03/060105 WO 03160105PCT/AU02/01768 5/8 2 4 EmrBa Mew~ -2.0 SD Days Post Inoculation I 1C 12 14 FIGURE c' 6 CL C. 4- 0 2 0 0 2 4 6 8 10 12 14 Days Post Vaccination FIGURE WO 03/060105 WO 03/60105PCT/A1J02/01768 6/8 12.00. 10.00 -I 9.00--i 8.00-- 600-1 4 00 J .001 2 4 0 a 10 12 14 Days Post Inorulation 8-r Slv M.-s 2.0 SE) DeAe lvM-r FIGURE control mice X4- vaccinated mice 0 2 4 6 8 10 12 14 16 1820 2224 2628 Days Post Challenge FIGURE 6WO 03/060105 WO 03/60105PCT/AU02/01768 7/8 Eont,- mice vacc.intd mice] 1 10 4 21 Days Post Challenge FIGURE 7A 0 control mice .1 10 14 21 Days Post Challenge FIGURE 7BWO 03/060105 WO 03/60105PCT/AU02/01768 8/8 200 0 control mice U vaccinated mice E150-___ E 100- E L 0- -1 10 14 21 Days Post Challenge FIGURE 8A 0 control mice U vaccinated mice S150 E 100 z LL. 50 0 -1 10 14 21 Days Post Challenge FIGURE 8BWO 031060105 WO 03160105PCT/AU02/01768 1- SEQUENCE LISTING <110> Delta Biotechnology Limited (all Cornford-Nairn, Renee (US only) Daggard, Grant Edward (US only) Mukkur, Trilochan Kanwaljit Singh Rossetti, Tony Robert (US only) states except US) (US only) <120> Defective entities and uses therefor <130> 2601959/VPA <140> Not yet assigned <141> 2002-12-30 <150> AU PR977G/01 <151> 2001-12-28 <160> 7 <170> Patentln version 3.1 <210> <211> <212> <213> <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> 1 942 DNA Bordetella pertussis misc feature n unknown nucleotide misc feature n unknown nucleotide misc feature (512) (512) n unknown nucleotide misc feature (523) n unknown nucleotide misc feature (527) (527) n unknown nucleotide misc feature (536) (536) n unknown nucleotideWO 03/060105 WO 03/60105PCT/A1102/01768 <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> <220> <221> <222> <223> <220> <2

CHANGE OF OWNERSHIP

New Name	Trilochan Kanwaljit Singh Mukkur	Old Name	University of Southern Queensland
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DRAWINGS

Defective entities and uses therefor

Details for Australian Patent Application No. 2002357406 (hide)

Owner Trilochan Kanwaljit Singh Mukkur

Inventors Daggard, Grant Edward; Rossetti, Tony Robert; Cornford-Nairn, Renee; Mukkur, Trilochan Kanwaljit Singh

Agent Fisher Adams Kelly

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C12N 15/52 (2006.01) Mutation or genetic engineering - Genes encoding for enzymes or proenzymes

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