Pheromonicin® Patent Summary

Pheromonicin Biotech Group (including entities in Beijing, Los Angeles and BVI) collectively hosts a cluster of 9 key invention patents covering Pheromonicin drug designs for major fields of anti bacteria, anti fungi, anti tumor cells and anti algae applications. The platform invention and technologies assure continuous patent protections through next 15 years, and rowing in variations, applications and extended years of coverage. Most Pheromonicin invention patents are originated in China. Most of them have PCT priorities expanded up to 80 world regions, among which 3 key patents are granted in USA, 1 key patent is granted in Australia, and 2 key patents are granted in Hong Kong by 2013, many are pending in other regions. The following samples some key invention patents already granted.

1. HHJC 海虹嘉诚案号：P09247/JJQ

China Patent 中国专利号：ZL200910157564 授权日 2012.06.20

本发明涉及“一种新型抗生素及其核苷酸序列、制备方法与应用”，属于生物医药领域，包括大肠菌素变构多肽与葡萄球菌信息素肽链，能特异地杀灭该抗生素特异性结合的致病菌而不会伤害人体正常细胞，大肠菌素变构多肽与葡萄球菌信息素线性联接，产生了抗金黄色葡萄球菌、表皮葡萄球菌以及绿脓杆菌的新型抗生素，抗菌效果是传统抗生素的千倍以上，而且不易产生耐药性，同时该新型抗生素克服了野生型大肠菌素使人体产生超敏反应的缺陷，使用起来更安全。

Translation: The present invention belongs to field of biology and medicine, and especially relates to a novel antibiotic, its nucleotide sequence, methods of construction and uses thereof. A novel antibiotic, wherein the end of any peptide of the allosteric colicin is connected linearly to the end of peptide of the Staphylococcus aureus pheromone AgrD I, AgrD II, AgrD III, AgrD IV or Staphylococcus epidermidis pheromone. Wherein the allosteric colicin being yielded by artificially mutating the amino acid residues G11A, H22R, A26G, V31L and H40K in the the peptide chain of wild type Colicin E1, Ia, Ib, A, B, N, or their ion channel-forming structural domain. In comparison with the traditional antibiotics, the novel antibiotics in the present invention are not likely to lead to drug resistance and cause hypersensitivity reaction.

2. HHJC 海虹嘉诚案号：P09299/JJQ

China Patent 中国专利号：ZL200810045212.6 授权日 2010.06.23

本发明提供一种抗炭疽多肽的基因、重组质粒、多肽及其应用与制备方法。将编码抗体模拟物的基因与编码重组突变炭疽杆菌蛋白抗原的基因可操作地连接，从而获得表达重组抗炭疽多肽的基因。将如上所述的编码抗体模拟物的基因经双链寡聚核苷酸点突变技术插入重组突变炭疽杆菌蛋白抗原基因即形成本发明的重组质粒。将获得的重组质粒转染入大肠杆菌 BL-21 工程菌中而获得可产生抗炭疽多肽的工程菌细胞；大量增菌、离心沉淀菌体、蔗糖一硫酸镁法提取含多肽上清、上清过柱纯化即可得到抗炭疽多肽。此种抗炭疽多肽可特异性的破坏炭疽杆菌毒素的生物活性，且不会攻击正常人体细胞。

Translation: A gene, recombinant plasmid and polypeptide of anthrax polypeptide as well as its preparation are provided in this invention. The gene coding antibody mimics is linked operationally with the gene coding recombinant mutant anthrax bacillus protein to get the gene of anthrax polypeptide. The gene coding antibody mimics mentioned above is inserted to antigen gene of recombinant mutant anthrax bacillus protein by double stranded oligonucleotide point mutation technology to form the recombinant plasmid of this invention. Escherichia coli BL-21 engineering bacteria are transfected with the recombinant plasmid to obtain the engineering bacteria cells which can

produce anthrax polypeptide. After bacteria propagation in large-scale, bacteria are centrifuged and extracted by sucrose-magnesium sulfate method to get supernatant containing polypeptide. Supernatant is treated with column purification to get anthrax polypeptide. This anthrax polypeptide can specifically undermine anthrax bacillus toxin bioactivity but cannot attack normal cells.

3. HHJC 海虹嘉诚案卷号：P11231/JJQ

China Patent 中国专利号：ZL200510020168.X 授权日 2007.05.09

本发明公开了一种新型抗真菌多肽及其制备方法，该重组抗真菌多肽含有可形成离子通道大肠菌素的离子通道结构域，以及白色念珠菌信息素。本发明的新型抗真菌多肽相较于现用抗真菌药物的优点在于，其直接在真菌细胞膜上形成离子通道来杀伤真菌，因此杀伤效率强于现用抗真菌药物数十倍；由于真菌难以通过突变-表达方式来修补该多肽在其胞膜上造成的几何损伤，因此该多肽不会诱导真菌产生传统的耐药性；由于该多肽对真菌是靶向性杀伤，因此它无现用抗真菌药物的毒副作用。

Translation: A new antifungal polypeptide and its preparation are published in this invention. This antifungal polypeptide contains candida albicans pheromone and colicine ion channel domain. Compared with the current antifungal drugs, the advantages of new antifungal polypeptideof the invention are as following: it kills fungal through directly forming ion channel on fungal cytomembrane, so its killing-efficiency is dozens of times higher than the current antifungal drug. The fungal is hard to repair physics damage on cytomembrane by mutation-expression, so the polypeptide won`t induce fungal with traditional drug-tolerance. Since the polypeptide kill fungal by targeting method, it has no toxic side effect as the current crop antifungal drug has.

4. HHJC 海虹嘉诚案卷号：P11231/JJQ

China Patent 中国专利号：ZL200510020168.X 授权日 2007.08.08

本发明公开了一种新型抗真菌多肽及其制备方法，该重组抗真菌多肽含有可形成离子通道大肠菌素的离子通道结构域，以及白色念珠菌信息素。本发明的新型抗真菌多肽相较于现用抗真菌药物的优点在于，其直接在真菌细胞膜上形成离子通道来杀伤真菌，因此杀伤效率强于现用抗真菌药物数十倍；由于真菌难以通过突变-表达方式来修补该多肽在其胞膜上造成的几何损伤，因此该多肽不会诱导真菌产生传统的耐药性；由于该多肽对真菌是靶向性杀伤，因此它无现用抗真菌药物的毒副作用。

Translation: A new antifungal polypeptide and its preparation are published in this invention. This antifungal polypeptide contains candida albicans pheromone and colicine ion channel domain. Compared with the current antifungal drugs, the advantages of new antifungal polypeptideof the invention are as following: it kills fungal through directly forming ion channel on fungal cytomembrane, so its killing-efficiency is dozens of times higher than the current antifungal drug. The fungal is hard to repair physics damage on cytomembrane by mutation-expression, so the polypeptide won`t induce fungal with traditional drug-tolerance. Since the polypeptide kill fungal by targeting method, it has no toxic side effect as the current crop antifungal drug has.

5. HHJC 海虹嘉诚案卷号：P09326/JJQ

China Patent 中国专利号：ZL200910092128.4 授权日 2012.02.15

本发明属于生物医药领域，特别是涉及“一种含抗体模拟物的新型抗生素及其制备方法与应用”，一种含抗体模拟物的新型抗生素，由大肠菌素 E1、Ia、Ib、A、B、N 或其水性孔道结构域及抗体模拟物构成，所述抗体模拟物是由免疫球蛋白的 VHCDR1 的羧基端连接 VHFR2 的氨基端，VHFR2

的羧基端再连接 VLCDR 的氨基端构成；所述免疫球蛋白特异性识别细菌膜孔蛋白。可用于制备抗抗脑膜炎双球菌、抗耐万古霉素肠球菌、抗耐甲氧西林金葡菌或抗多重耐药绿脓杆菌的药物中。

Translation: The present invention belongs to field of biology and medicine, and especially relates to a novel antibiotic comprising an antibody mimetic antibody, its preparation methods and uses thereof. A novel antibiotic comprising a antibody mimetic covalently bonded to the carboxyl end of a colicin polypeptide or a channel-forming domain polypeptide of a colicin, wherein said colicin is selected from the group consisting of Colicin E1, Ia, Ib, A, B, N; wherein said antibody mimetic being yielded by fusing two complementarity determining regions (CDRs), VHCDR1 and VLCDR3 through a cognate framework region (VHFR2) of an immunoglobulin; wherein said the immunoglobulin specifically recognizes the bacterial porins. Its antibacterial ability is a thousandfold powerful than normal antibiotics. Due to its unique action mechanism, drug resistance resulted in mutation can hardly be acquired by pathogenic bacteria. And the antibiotic will not hurt normal human cells when it kills pathogenic bacteria. Therefore, it can be used for manufacturing antibacterial medicament of killing Neisseria meningitidis, vancomycin-resistant Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, multidrug-resistance Pseudomonas aeruginosa or Mycobacterium tuberculosis.

6. HHJC 海虹嘉诚案号：P09298/JJQ

China Patent 中国专利号：ZL200410081446.8 授权日 2006.09.13

本发明提供一种抗 **EB** 病毒所致肿瘤的基因、重组质粒和多肽。将编码诱导多肽的基因与大肠菌素基因可操作地连接，从而获得表达重组抗肿瘤多肽的核苷酸序列。将如上所述的编码诱导多肽的核苷酸序列经双链寡聚核苷酸点突变技术插入大肠菌素基因即形成本发明的重组质粒。将获得的重组质粒转染入大肠杆菌 **TG1** 工程菌中而获得可产生重组抗肿瘤多肽的工程菌细胞；大量增菌、离心沉淀菌体、超声破碎、高速离心沉淀破碎菌体、取上清进行处理即可得到重组抗肿瘤多肽。本发明所述抗肿瘤多肽具有特异的靶向性，特异杀灭实体肿瘤的效率高于传统抗肿瘤药物，而不会攻击正常细胞，其毒性和不良反应远低于传统抗肿瘤药物。

Translation: A gene, recombinant plasmid and polypeptide of anti cancer caused by EB virus are provided in the invention. The gene coding the guide polypeptide is linked operationally with colicine gene to obtain the nucleotide sequence of recombinant anti-cancer polypeptide. The nucleotide sequence mentioned above is inserted to colicine gene by double stranded oligonucleotide point mutation technology to form recombinant plasmid of this invention. Escherichia coli TG1 engineering bacteria are transfected with the recombinant plasmid to obtain the engineering bacteria cells which can produce recombinant anti-cancer polypeptide. After bacteria propagation in large-scale, bacteria are centrifuged and shattered by ultrasonic. Its supernatant is treated to get the recombinant anti-cancer polypeptide. It`s demonstrated in this invention that, the anti-cancer polypeptide has specific targeting with its solid cancer specific killing rate higher than traditional anti-cancer drug and without attacking normal cells; its toxicity and untoward effects are much lower than traditional anti-cancer drug.

7. HHJC 海虹嘉诚案卷号：P10084/JJQ

China Patent 中国专利号：ZL200510021661.3 授权日 2009.05.06

本发明公开了一种小型化抗耐药金黄色葡萄球菌多肽，该多肽含有可形成离子通道大肠菌素的通道结构域，以及金黄色葡萄球菌信息素。本发明还公开了编码上述多肽的核苷酸序列以及含有所述核苷酸序列的重组质粒。本发明所述多肽不会诱导细菌产生传统的耐药性，其机理是通过直接在靶细菌的胞膜上形成离子通道而杀死细菌的,本发明所述多肽的抗菌谱更为专一，只杀灭金黄色葡萄球菌， 而不杀灭大肠杆菌类革兰氏阴性菌，且杀菌效力很强，试验表明对抗

耐药金黄色葡萄球菌感染的治疗效果至少是苯唑西林治疗效果的 500 倍。同时还可作为 0-内酰胺类抗菌素的增效剂和细菌毒素抑制剂使用。

Translation: A small-scale anti-drug tolerance staphylococcus aureus (SA) polypeptide is issued in this invention. This polypeptide contains channel domain of forming ion channel colicine and SA pheromone. Nucleotide sequence coding the polypeptide and recombinant plasmid containing the nucleotide sequence are also published in this invention. The polypeptide mentioned in this invention cannot induce bacteria with traditional drug tolerance, and its mechanism is that it can form ion channel directly on cytomembrane of targeting bacteria to kill the bacteria. The antibacterial spectrum of thepolypeptide of the invention is specific for SA instead of coliform bacteria etc. gram-negative bacteria, and strong in sterilization effect. It`s indicated by experiments that, its therapy effect on anti-drug tolerance SA infection is 500 times higher than oxazocilline at least. Meanwhile, the polypeptide can be used as potentiator for 0-Lactam antibiotics and inhibitor for bacteriotoxin.

8. HHJC 海虹嘉诚案卷号：P09551-JJQ

China Patent 中国专利号 ZL200910242838.0 授权日 2013.3.20

本发明"一种新型抗 EB 病毒所致肿瘤多肽及其应用与制备方法 "，属于抗肿瘤药物领域，由可形成离子通道的大肠菌素变构多肽与抗 EB 病毒抗体多肽或者抗 EB 病毒抗体的模拟抗体多肽构成，所述可形成离子通道的大肠菌素变构多肽由野生型大肠菌素 E1、Ia、Ib、A、B、N 或其水性孔道结构域的肽链突变了氨基酸残基 G11A、H22G、A26G、V31L 和 H40D 而获得，所述抗 EB 病毒抗体的氨基酸序列与 ATCC HB-168 杂交瘤分泌的单克隆抗体相同。为治疗 EB 病毒所致肿瘤提供一种改进的杀伤力强、安全性高，高特异性且致敏可能性较低的药物及其制备方法。

Translation: The present invention of "novel polypeptide against tumor caused by EB virus and use and preparation method thereof" belongs to the field of anti-tumor agents. The polypeptide is formed by a mutant polypeptide of colicin which can form ion channels with a polypeptide of anti-EB virus antibody or a polypeptide of anti-EB virus antibody mimetics, the mutant polypeptide of colicin which can form ion channels is obtain by mutation of amino acid residues of G11A, H22G, A26G, V31L, and H40D to peptide chain of wild-type colicin E1, Ia, Ib, A, B, N or aqueous channel domain thereof, the amino acid sequence of the polypeptide of anti-EB virus antibody is the same as the polypeptide of antibody secreted by hybridoma of ATCC HB-168. The present invention provides an improved medicine for the treatment of tumor caused by EB virus which has high killing ability, high specificity, and low possibility of allergy, and provides a method for the preparation thereof.

9. HHJC 海虹嘉诚案卷号：P09300/JJQ

China Patent 中国专利号 ZL200710050926.1 授权日 2013.5.6

本发明公开了一种新型抗农作物真菌多肽及其制备方法，该重组抗农作物真菌多肽含有可形成离子通道大肠菌素，以及白色念珠菌信息素。本发明的新型抗农作物真菌多肽相较于现用农业抗真菌药物的优点在于，其直接在真菌细胞膜上形成离子通道来杀伤真菌，因此杀伤效率强于现用农业抗真菌药物数十倍；由于真菌难以通过突变－表达方式来修补该多肽在其胞膜上造成的几何损伤，因此该多肽不会诱导真菌产生传统的耐药性；由于该多肽对真菌是靶向性杀伤，因此它无现用抗农业真菌药物的毒副作用。

Translation: A new antifungal polypeptide used in crop and its preparation are published in this invention. This antifungal polypeptide contains Candida albicans pheromone and Colicine channel-forming domain which is available to form ion channel. Compared with the current crop antifungal drugs, the advantages of the antifungal polypeptide of the invention are as following: it kills

fungal through directly forming ion channels on fungal cytomembrane. Its killing-efficiency is dozens of times higher than the current crop antifungal drug. Because the fungal is hard to repair physical damage on its cytomembrane by mutation-expression method. The polypeptide may not result in traditional drug-tolerance in fungal. The polypeptide kill fungal by targeting method, so it's not as current crop antifungal drugs possessing toxic side-effect.

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10. US Patent 美国专利 No. 6942993 授权日 2005.09.13

Engineered antibiotic peptides and the preparation thereof are provided. The engineered antibiotic peptides, designated pheromonicins, are prepared by linking different bacteriocins or their functional domains with bacterial pheromones. Also provided are methods for treating bacterial infections by use of the antibiotic peptides.

Translation: 本专利提供一种工程抗菌肽及其制备方法。该抗菌肽，命名为信息素，是通过细菌信息素连接各种细菌素或它们的功能结构域制备制备而得。同时还提供了使用该抗菌肽治疗细菌感染的方法。

11. HHJC 海虹嘉诚案卷号: P10103/JJQ

US application No 美国专利申请号: 11/338117 授权日 2011.03.29

The present invention is directed to fusion peptides comprising a fungal targeting agent and a channel-forming domain consisting essentially of amino acids 451-626 of colicin Ia, as well as the polynucleotides encoding the peptides of the invention. The fusion peptides of the present invention are particularly useful for the treatment of fungal infections in a wide variety of organisms.

Translation: 本发明关于一种由真菌靶向剂和至少由大肠杆菌素 Ia 的 451-626 位氨基酸组成的通道形成结构域构成的融合肽，以及编码本发明所述融合肽的多核苷酸。本发明的所述融合肽对治疗多种生物体中的真菌感染特别有效。

12. HHJC 海虹嘉诚案卷号 P09366/JJQ

US Application No. 美国专利申请号 11/297464

US Patent 美国专利 8367066 授权日 2012.10.6

The present invention relates to molecules that are capable of killing cells. The molecules comprise a targeting agent and a channel-forming moiety. The molecules may be polypeptides. The present invention also relates to polynucleotide sequences encoding the polypeptides of the invention. In a preferred embodiment, the channel-forming moiety comprises a colicin and the targeting agent is an antibody. Methods of treatment by administering the molecules of the present invention are also provided.

Translation: 本发明涉及可以杀死细胞的分子。该分子由靶向剂和通道形成部分构成。该分子可以是多肽。本发明还涉及编码本发明的多肽的核苷酸序列。在优选的实施方式中，通道形成部分包含一种大肠菌素，靶向剂则是一种抗体。本发明还提供通过给予本发明的该分子的治疗方法。

13. HHJC 海虹嘉诚案卷号 PC10581-P11878-CN-AU-JJQ

Australia Patent 澳大利亚专利 2010291640 授权日 2013.5.2

The present invention belongs to field of biology and medicine, and especially relates to a novel antibiotic comprising an antibody mimetic antibody, its preparation methods and uses thereof. A novel

antibiotic comprising a antibody mimetic covalently bonded to the carboxyl end of a colicin polypeptide or a channel-forming domain polypeptide of a colicin, wherein said colicin is selected from the group consisting of Colicin E1, Ia, Ib, A, B, N; wherein said antibody mimetic being yielded by fusing two complementarity determining regions (CDRs), VHCDR1 and VLCDR3 through a cognate framework region (VHFR2) of an immunoglobulin; wherein said the immunoglobulin specifically recognizes the bacterial porins. Its antibacterial ability is a thousandfold powerful than normal antibiotics. Due to its unique action mechanism, drug resistance resulted in mutation can hardly be acquired by pathogenic bacteria. And the antibiotic will not hurt normal human cells when it kills pathogenic bacteria. Therefore, it can be used for manufacturing antibacterial medicament of killing Neisseria meningitidis, vancomycin-resistant Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, multidrug-resistance Pseudomonas aeruginosa or Mycobacterium tuberculosis.

Translation: 本发明属于生物医药领域，特别是涉及“一种含抗体模拟物的新型抗生素及其制备方法与应用”，一种含抗体模拟物的新型抗生素，由大肠菌素 E1、Ia、Ib、A、B、N 或其水性孔道结构域及抗体模拟物构成，所述抗体模拟物是由免疫球蛋白的 VHCDR1 的羧基端连接 VHFR2 的氨基端，VHFR2 的羧基端再连接 VLCDR 的氨基端构成；所述免疫球蛋白特异性识别细菌膜孔蛋白。可用于制备抗抗脑膜炎双球菌、抗耐万古霉素肠球菌、抗耐甲氧西林金葡菌或抗多重耐药绿脓杆菌的药物中。

14. HHJC 海虹嘉诚案卷号 P11846CN-HK/JJQ（对应 PC09622）

Hong Kong Patent Application 香港申请号 11113462.9 优先权日 2009.12.17

本发明“一种新型抗 EB 病毒所致肿瘤多肽及其应用与制备方法 ”，属于抗肿瘤药物领域，由可形成离子通道的大肠菌素变构多肽与抗 EB 病毒抗体多肽或者抗 EB 病毒抗体的模拟抗体多肽构成，所述可形成离子通道的大肠菌素变构多肽由野生型大肠菌素 E1、Ia、Ib、A、B、N 或其水性孔道结构域的肽链突变了氨基酸残基 G11A、H22G、A26G、V31L 和 H40D 而获得，所述抗 EB 病毒抗体的氨基酸序列与 ATCC HB-168 杂交瘤分泌的单克隆抗体相同。为治疗 EB 病毒所致肿瘤提供一种改进的杀伤力强、安全性高，高特异性且致敏可能性较低的药物及其制备方法。

Translation: The present invention of “novel polypeptide against tumor caused by EB virus and use and preparation method thereof” belongs to the field of anti-tumor agents. The polypeptide is formed by a mutant polypeptide of colicin which can form ion channels with a polypeptide of anti-EB virus antibody or a polypeptide of anti-EB virus antibody mimetics, the mutant polypeptide of colicin which can form ion channels is obtain by mutation of amino acid residues of G11A, H22G, A26G, V31L, and H40D to peptide chain of wild-type colicin E1, Ia, Ib, A, B, N or aqueous channel domain thereof, the amino acid sequence of the polypeptide of anti-EB virus antibody is the same as the polypeptide of antibody secreted by hybridoma of ATCC HB-168. The present invention provides an improved medicine for the treatment of tumor caused by EB virus which has high killing ability, high specificity, and low possibility of allergy, and provides a method for the preparation thereof.

15. HHJC 海虹嘉诚案卷号 P11846CN-HK/JJQ（对应 PC09622）

Hong Kong Patent Application 香港申请号 11113462.9 优先权日 2012.8.31

本发明属于生物医药领域，特别是涉及“一种含抗体模拟物的新型抗生素及其制备方法与应用”，一种含抗体模拟物的新型抗生素，由大肠菌素 E1、Ia、Ib、A、B、N 或其水性孔道结构域及抗体模拟物构成，所述抗体模拟物是由免疫球蛋白的 VHCDR1 的羧基端连接 VHFR2 的氨基端，VHFR2 的羧基端再连接 VLCDR 的氨基端构成；所述免疫球蛋白特异性识别细菌膜孔蛋白。可用于制备抗抗脑膜炎双球菌、抗耐万古霉素肠球菌、抗耐甲氧西林金葡菌或抗多重耐药绿脓杆菌的药物中

Translation: The present invention belongs to field of biology and medicine, and especially relates to a novel antibiotic comprising an antibody mimetic antibody, its preparation methods and uses thereof. A novel antibiotic comprising a antibody mimetic covalently bonded to the carboxyl end of a colicin polypeptide or a channel-forming domain polypeptide of a colicin, wherein said colicin is selected from the group consisting of Colicin E1, Ia, Ib, A, B, N; wherein said antibody mimetic being yielded by fusing two complementarity determining regions (CDRs), VHCDR1 and VLCDR3 through a cognate framework region (VHFR2) of an immunoglobulin; wherein said the immunoglobulin specifically recognizes the bacterial porins. Its antibacterial ability is a thousandfold powerful than normal antibiotics. Due to its unique action mechanism, drug resistance resulted in mutation can hardly be acquired by pathogenic bacteria. And the antibiotic will not hurt normal human cells when it kills pathogenic bacteria. Therefore，it can be used for manufacturing antibacterial medicament of killing Neisseria meningitidis, vancomycin-resistant Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, multidrug-resistance Pseudomonas aeruginosa or Mycobacterium tuberculosis.

