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Wolbachia of arthropods and filarial nematodes: biology and applications

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Wolbachia is a group of obligatory intracellular gram-negative bacteria. This bacterium is responsible for manipulation of host reproduction in many arthropod species and involved in embryonic and larval development, adult female fertility, and survival in filarial nematode. The applied biology of *Wolbachia* and modification of pest and vector species using *Wolbachia* have been studied in order to suppress or modify natural populations. In addition, *Wolbachia* has been used as a novel chemotherapeutic target for filariasis control program. This article reviews the biology of *Wolbachia* in arthropods and filarial nematodes, including recent advance and future directions of using *Wolbachia* as a target for vector populations control and filariasis drug target.

Keywords : *Wolbachia,* arthropods, filarial nematodes.

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Objectives :

1. To understand the biology of *Wolbachia* in arthropods as well as in filarial nematodes:
2. To report the recent advance and future direction of *Wolbachia* studies and researches.

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ศิวะพงษ์ สังข์ประดิษฐ์, สุรางค์ นุชประยูร. แบคทีเรียโวลบาเชียของแมลงและพยาธิกลุ่มฟิลาเรีย: ชีววิทยาและการประยุกต์. จุฬาลงกรณ์เวชสาร 2553 พ.ย. – ธ.ค.; 54(6): 605 – 21

โวลบาเชียเป็นกลุ่มแบคทีเรียชนิดแกรมลบที่ต้องอาศัยอยู่ในเซลล์ แบคทีเรียชนิดนี้มีบทบาทหน้าที่เกี่ยวข้องกับการควบคุมการสืบพันธุ์ของสัตว์ขาปล้องหลายชนิด รวมถึงการพัฒนาของเอ็มบริโอและตัวอ่อนของพยาธิ การเจริญพันธุ์ของพยาธิเพศเมีย และการมีชีวิตรอดของพยาธิกลุ่มฟิลาเรีย การศึกษาชีววิทยาประยุกต์ของแบคทีเรียโวลบาเชียสามารถนำมาดัดแปลงคุณสมบัติของแมลงศัตรูพืชและแมลงนำโรค เพื่อลดหรือปรับเปลี่ยนจำนวนประชากรของแมลงดังกล่าวในธรรมชาติ นอกจากนี้แบคทีเรียโวลบาเชียยังเป็นเป้าหมายใหม่ในการควบคุมโรคที่เกิดจากพยาธิกลุ่มฟิลาเรีย ในบทความนี้นำเสนอชีววิทยาของแบคทีเรียโวลบาเชียในสัตว์ขาปล้องและพยาธิกลุ่มฟิลาเรีย รวมทั้งความก้าวหน้าและทิศทางของการศึกษาวิจัย ได้แก่ การใช้แบคทีเรียโวลบาเชียในการเป็นเป้าหมาย เพื่อควบคุมแมลงพาหะและการพัฒนายารักษาโรคที่เกิดจากพยาธิกลุ่มฟิลาเรีย

คำสำคัญ : *แบคทีเรียโวลบาเชีย, สัตว์ขาปล้อง, พยาธิกลุ่มฟิลาเรีย.*

Wolbachia is a genus of the class Alphaproteobacteria and belongs to the order Rickettsiales. These gram-negative intracellular bacteria are found widespread in arthropods as well as filarial nematodes.[1-3] Based on the 16S rDNA gene and the protein-coding gene (*groEL*) sequence analysis, it has been organized into the family Anaplasmataceae which also includes all species of the genera *Ehrlichia*, *Anaplasma*, *Cowdria*, and *Neorickettsia.* [4] In contrast to members of the family Rickettsiaceae, which grow in the cytoplasm or nucleus of their eukaryotic host cells, members of the Anaplasmataceae family replicate while enclosed in a eukaryotic host cell membrane-derived vacuole. [5]

In the absence of a formal nomenclatural system, the *Wolbachia* community currently refers to the different lineages as "supergroups". [6] In addition, the species name, *Wolbachia pipientis*, remains single until new data are generated in different research areas (e.g., comparative genomics, molecular phylogenetics, and screening for *Wolbachia* in new hosts). The DNA-sequence-based methods, including phylogenetic analysis based on 16S rDNA*, dnaA, ftsZ, gltA, groEL* and *wsp* genes have been employed for taxonomic classification. [3, 7, 8] At present, 11 taxonomic supergroups are described for the genus *Wolbachia* by their places in molecular phylogenies. These 11 supergroups are labeled A-K alphabetically which include A and B found in various arthropods, C (*Onchocerca* spp. and *Dirofilaria* spp.) and D (*Wuchereria bancrofti*, *Brugia* spp., and *Litomosoides* spp.) are restricted to filarial nematodes, E containing *Wolbachia* from springtails (*Folsomia candida*), F containing *Wolbachia* from termites (*Kalotermes flavicollis* and *Microcerotermes* spp.), weevils (*Rhinocyllus conicus*), and the filarial nematode *Mansonella ozzardi*, and G and H found in *Wolbachia* from Australian spiders and the Pacific dampwood termites (*Zootermopsis angusticollis* and *Z. nevadensis*), respectively. [2, 3, 6, 8-11] The more recently proposed supergroups, I, J, and K, are containing *Wolbachia* from cat flea (*Ctenocephalides felis*), filarial nematode (*Dipetalonema gracile*), and spider mite (*Bryobia* spp.), respectively. [12]

Insect *Wolbachia:* reproductive bacterial parasites of arthropods

In 1924s, intracellular bacteria were first reported as Rickettsia-like microorganisms, within the ovaries and testes of the mosquito *Culex pipiens* by Hertig and Wolbach. These bacteria were subsequently named *Wolbachia pipientis.* [13] Phylogenies based on 16S rDNA sequences have confirmed that morphological similarities to the Rickettsiae are based on phylogenetic relatedness. [14, 15] It is estimated that these bacteria infect at least 20% of all insect species. [16] Recently, data reported from a beta binomial model suggest that *Wolbachia*-infected species are estimated to be 66%, and within one species the frequency of *Wolbachia* infection is either very high (>90%) or very low (<10%). [17] Infections by *Wolbachia* of the reproductive tissues of arthropods are transmitted maternally from infected females to their progeny via the egg cytoplasm, and have evolved to manipulate host reproduction. [18]

Research interest in *Wolbachia* was initially triggered when it was discovered that this organism can cause several kinds of reproductive change in arthropod reproduction. [1, 19] These reproductive manipulations include: (1) inducing embryonic lethality

in insect embryos that result when uninfected females are mated to infected males (cytoplasmic incompatibility); [20-22] (2) inducing parthenogenesis in infected insects (the ability of infected unfertilized insect eggs to successfully develop into functional female adults); [23, 24] and, (3) overriding chromosomal sex determination in crustaceans to convert infected genetic males into functional phenotypic females (feminization of genetic males). [25, 26] Each of these reproductive effects enhances transmission of *Wolbachia* to the arthropod population which is not yet infected with *Wolbachia*. [1, 19]

The reproductive abnormalities induced by *Wolbachia* are of interest to apply biologists, who attempt novel means to genetically manipulate populations of insect pests that are important for economic and health reasons. [27] *Wolbachia*-induced cytoplasmic incompatibility can be used as a tool for insect pest population control and as a driven system to release desirable genotypes into mosquito populations to control disease transmission. For instance, in the control of transmission of vector-borne diseases, a genetic approach would target expression of foreign anti-parasitic or anti-viral gene products in *Wolbachia* harbored by insects. Recently, a life-shortening strain of virulent *Wolbachia* (*w*MelPop) was transferred into *Aedes aegypti*, the major mosquito vector of dengue, in order to decrease its life span and disease transmission. [28] Parasitoids used in biological control of insects may be more effective when infected with parthenogenesis *Wolbachia*. [29] *Wolbachia* and its hosts are ideal candidates for studies to elucidate the mechanisms of host-parasite relationships and the evolution of infectious diseases, specifically host resistance, parasite virulence and transmission dynamics. [30, 31]

Recently, lateral or horizontal gene transfer (LGT or HGT) occurring between *Wolbachia* and multicellular eukaryotic host genome has been described. [32-34] The presence of *Wolbachia*-derived DNA sequences in a beetle [35] and a filarial nematode [36] was investigated by screening whole-genome shotgun data from a wide range of nematodes and arthropods for nuclear insertions of *Wolbachia* DNA. In addition, fragments of *Wolbachia* DNA were identified in the introns of a previously sequenced gene from a human filarial nematode, *B. malayi* [37], and an animal filarial nematode, *Dirofilaria immitis* [32] However, the consequence of endosymbiont-host LGTs has not yet been studied in detail and remains poorly understood.

Nematode *Wolbachia*: mutualistic relationships

At the beginning of the 1970s, electron microscopy studies of various filarial nematodes, including *D. immitis*, *B. pahangi*, *B. malayi* and *Onchocerca volvulus*, revealed the presence of intracellular bacteria. [38-41] In 1990s, two decades after the discovery of *Wolbachia*, based on DNA sequence data, intracellular bacteria have been identified as being closely related to *Wolbachia*. [3, 42] In addition to electron microscopy, molecular techniques were employed for the surveys of *Wolbachia* are based on PCR, followed by a sequencing technique and immunohistochemistry. [18] Although it occurs in varying proportions between individual worms and different developmental stages, *Wolbachia* are found throughout the entire life-cycle stages of the filarial nematode hosts. [40, 41, 43, 44] Within the body of filarial nematodes, the bacteria are restricted to the lateral

chords of the adults and the reproductive tissues of the female (e.g., oogonia, oocytes, embryos and microfilariae). However, *Wolbachia* have not been detected in the male reproductive system. [45, 46] These findings suggest that the bacteria are vertically transmitted through the cytoplasm of the egg, and not through the sperm. [40, 41]

It now is known that *Wolbachia* are widespread in filarial nematodes. Of the 14 genera so far examined, *Wolbachia* have been revealed in the 8 genera of a total of 19 filarial species (Tables 1 and 2). [3, 42, 47-52] These filarial nematodes include, namely, *B. malayi*, *W. bancrofti*, and *O. volvulus*; all these species are important to human health; and *D. immitis,* which causes dog heartworm disease. [3, 42, 47] Recently, *Wolbachia* has been identified in plant-parasitic nematode, *Radopholus similes,* and is designated to the supergroup I. So far, the molecular functions of *Wobachia* in plant tissues still remain unknown. [53]

The presence of *Wolbachia* in filarial nematodes appears to be limited to the family Onchocercidae (Table 1). Within this family, the positive species belong to the subfamilies Onchocercinae and Dirofilariinae, while *Wolbachia* are found to be negative for the subfamilies Waltonellinae and Setarinae. However, there are both positive and negative species in the Onchocercinae and Dirofilariinae (Table 2). In these subfamilies, two filarial species that are pathogenic to humans, *Loa loa* and *Mansonella perstans*, as well as the rodent filaria *Acanthocheilonema viteae*, the carnivore filaria *A. reconditum*, the bat filaria *Litomosoides yutajensis*, the deer filaria *O. flexuosa*, and the reptile filaria *Foleyella furcata* appear to be *Wolbachia* free. [3, 47, 50-56] Based on the results of screening for *Wolbachia* in nematodes outside the order Spirurida, there is no evidence of the presence of *Wolbachia.* [57, 58] This finding is consistent with the hypothesis that *Wolbachia* entered the nematode phylum once, in an ancestral lineage of filarial nematodes.

Table 1. Detection of *Wolbachia* in the genera of filarial nematodes.

Family	Subfamily	No. genera examined	Results for *Wolbachia*	
			Positive	Negative
Filariidae	Filarinae	1	-	1
Onchocercidae	Onchocercinae	8	5	3
	Dirofilariinae	3	1	2
	Waltonellinae	1	-	1
	Setarinae	1	-	1
	Oswaldofilariinae	1	-	1
	Icosiellinae	0		
	Splendidofilariinae	0		
	Lemdaninae	0		

Table 2. Distribution of *Wolbachia* in filarial nematodes.

Family	Subfamily	Genus	Presence	Absence
Filariidae	Filarinae	*Filaria*	-	*F. martis*
Onchocercidae	Onchocercinae	*Brugia*	*B. malayi*	-
			B. pahangi	
			B. timori	
		Wuchereria	*W. bancrofti*	
		Litomosoides	*L. sigmodontis*	*L. yutajensis*
			L. brasileiensis	
			L. galizai	
			L. hamletti	
		Dipetalonema	*D. gracile*	
		Litomosa	*L. westi*	
		Onchocerca	*O. volvulus*	*O. flexuosa*
			O. ochengi	
			O. gutturosa	
			O. gibsoni	
			O. lupi	
			O. cervicalis	
		Mansonella	*M. ozzardi*	*M. perstans*
		Acanthocheilonema	-	*A. viteae*
				A. reconditum
Dirofilariinae		*Dirofilaria*	*D. immitis*	
			D. repens	
		Foleyella	-	*F. furcata*
		Loa	-	*L. loa*
Waltonellinae		*Ochoterenella*	-	*Ochoterenella sp.*
Oswaldofilariinae		*Piratuba*	-	*P. scaffi*
Setarinae		*Setaria*	-	*S. equine*
				S. labiatopapillosa
				S. tundra

Based on the distribution of *Wolbachia,* it is placed in the taxonomy of filarial nematodes. The hypotheses on their evolution is: (1) *Wolbachia* may have been ancestrally absent from the lineages leading to *Filaria martis*, *Ochoterenella* spp., and *Setaria* spp.; (2) *Wolbachia* may have been acquired at one time in the lineage leading to the Onchocercinae/Dirofilariinae, and current negative species in these subfamilies are the results of secondary losses; (3) *Wolbachia* may have been acquired several times along various lineages of the Onchocercinae/Dirofilariinae; in this case, negative species in these subfamilies may represent either a primitive absence of the symbiosis or the effect of a secondary loss. [51, 59, 60]

Nematode *Wolbachia* morphology is pleomorphic coccobacilli, appearing either as cocci (0.3 - 0.8 μm in diameter) or short rods (up to 0.8 μm in diameter and 1.5 μm in length) [40] and less than 0.2 μm in size to greater than 4 μm in length. [46] Each *Wolbachia* cell lies in an individual vacuole enveloped by three layers of membranes. The outer layer is a host-derived membrane, followed by the outer cell wall of the bacteria, and the innermost layer consists of the plasma membrane of the bacteria. [42, 61] However, a few *Wolbachia* cells can also be observed to be within a host-derived vacuole. [41, 62] *Wolbachia* may divide by binary fission, the most common mode of replication in bacteria, and possibly by a more complicated method which is similar to the developmental cycle of Chlamydia, a *Wolbachia*-related organism. [46] This process is accompanied by corresponding changes within the organism. They appear to be a condensation of cytosol, formation of dense inclusions that may coalesce and form smaller entities within the parent organism. The smaller individuals will grow and develop to bacterial forms. Evidence of *Wolbachia* undergoing division is always reported in the adult female of filarial nematodes, especially in the reproductive tissues. [41, 46]

Quantification of *Wolbachia* numbers in different developmental stages has been studied in *B. malayi.* [43, 44] In blood-stage microfilariae (L1) and the mosquito vectors larval stages (L2 and L3), the numbers of *Wolbachia* remain constant with the lowest ratios of *Wolbachia*/nematode DNA. However, the *Wolbachia*/nematode ratio increases dramatically within the first week of infection of the definitive host; the ratio is the highest here out of all life-cycle stages. In female worms, *Wolbachia* copy numbers increase as the worms mature and their ovaries and embryos become infected. [43] Further studies on the dynamics of population levels in other filarial species are ongoing and should serve to further define the key features of the symbiotic association. A recent study comparing the different 'forest' and 'savanna' strains of *O. volvulus* found a significantly greater ratio of *Wolbachia*/nematode DNA in the severe, ocular disease-causing 'savanna' strain, supporting the role of the *Wolbachia* in the pathogenesis of ocular onchocerciasis. [63]

In both lymphatic filariasis and onchocerciasis, *Wolbachia* have been proposed for their ability to induce host inflammatory response and cause pathogenesis. [59, 64] Filariasis patients could be exposed to *Wolbachia* - either products released by the adult or those by the larval stages dying after chemotherapy and destroyed by the host. Lipopolysaccharide (LPS), lipoprotein, and groEL molecules are associated with the innate and adaptive immune activation. They are engaged with monocyte/

macrophage toll-like receptors (TLR2 and TLR6), and induce proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-12, and specific immunoglobulins production. [65-67] In addition, free *Wolbachia* or *Wolbachia* in egg fragments are slowly released from the uterus during the life span of the female. In addition, the soluble *Wolbachia*'s products and the small forms (elementary body analogues), may be transported via nematode excretory canals. [46]

The recent completion of genome sequencing and the annotation of the metabolic pathways of *Wolbachia* from *B. malayi* (*w*Bm) have identified important candidates for the dependency of symbiosis. [68] In comparison with the insect *Wolbachia* and related *Rickettsia*, the genome of *Wolbachia* from *B. malayi* is reduced in size, a feature common to the lifestyle of other endosymbiotic bacteria. [69-71] However, *Wolbachia* contains more intact metabolic pathways, which may be important in contributing to the welfare and fecundity of its host. The ability to provide riboflavin, flavin adenine dinucleotide (FAD), heme, and nucleotides is likely the bacterial contribution, whereas the host nematode provides amino acids required for bacterial growth with the exception of the only amino acid synthesized by the bacteria, meso-diaminopimelate, a major component of peptidoglycan. [59] Other features include a common type IV secretion system. [72, 73] and an abundance of ankyrin domain containing proteins, which could regulate the host gene expression as suggested for *Ehrlichia phagocytophilia* AnkA. [74, 75] Glutathione biosynthesis genes may be a source of glutathione for the protection of the host nematode from oxidative stress or immunological effector molecules. Heme from *Wolbachia* could be critical to worm embryogenesis, molting, and reproduction, which are regulated by ecdysteroid-like hormones. [76, 77] Depletion of *Wolbachia* might therefore stop production of these hormones and block embryogenesis. Alternatively or in addition, *Wolbachia* may be an essential source of nucleotides during embryogenesis. Thus, the achievement of the *w*Bm genome provides useful information that may increase the understanding of the molecular basis for endosymbiosis between *Wolbachia* and filarial nematodes. The novel and test drugs already registered for use in humans, which might inhibit key biochemical pathways in *Wolbachia* that could lead to the sterility or killing of the adult worms, will be screened for these properties. [59, 78-80]

Wolbachia as a novel filarial drug target

The efficacy of tetracycline and its derivative to diminish *Wolbachia*, which is essential for larval molting, adult female worm fertility, and adult survival in those filarial species that harbour them, were shown in several animal models of filariasis. [81] The African Program of Onchocerciasis Control (APOC) and the Onchocerciasis Elimination Program for the Americas (OEPA) have used 200 mg/day doxycycline for 6 weeks in onchocerciasis patients to sterile female worm and obtain macrofilaricidal effect. [82] In addition, the Global Program for Elimination of Lymphatic Filariasis (GPELF), anti-*Wolbachial* chemotherapy has been used as an alternative strategy for controlling lymphatic filariasis. In bancroftian and brugian filariasis, 3 [83], 4 [84], 6 [85, 86], and 8 [87] -week courses of treatment with 100 or 200 mg/day of doxycycline alone or in combination with (ivermectin or

albendazole), result in a macrofilaricidal effect, a decrease microfilaremic level, reduce *Wolbachia* copy number in the microfilariae, and an abatement in drug adverse reactions. More potent and short-term therapy of anti-*Wolbachial* and anti-filarial chemotherapeutic agents should be screened and identified. [80, 88] It has been suggested that tigecycline, a new class of glycylcycline antibiotic with similar structure to tetracycline, be tested against experimental filarial infections. [89] Since, doxycycline has limited use in pregnant and breastfeeding women, and children under the age of nine [82], rifampicin, which has anti-*Wolbachial* and anti-filarial activities could be used as an alternative regimen. [90] In addition, the macrofilaricidal activity of human lymphatic filariasis using a combination of doxycycline and rifampicin in a 3-week course has been studied. [82]

There is an urgent need to discover alternative anti-*Wolbachial* treatments that may be facilitated by identification of new drug targets in this endosymbiont. For example, in the *w*Bm genome analysis, it was found that this organism lacks pyruvate kinase (PK) and may alternately employ enzyme pyruvate phosphate dikinase (PPDK). This enzyme converts phosphate to ATP in the glycolysis pathway and could be inhibited by millimolar concentrations of imidodiphosphate. [91] A *Wolbachia* putative cofactor-independent phosphoglycerate mutase (iPGM) has also been predicted and identified from the *w*Bm genome sequence. The iPGM protein stimulates the transferring of the phosphoryl group between monophosphoglycerates through a phosphoserine intermediate. [92] iPGM represents an interesting *Wolbachia* drug target because it has a unique sequence and structure compared with the mammal cofactor-dependent phosphoglycerate mutase (dPGM). [93] The identification of *w*Bm–PPDK and *w*Bm–iPGM makes these enzymes an attractive and novel *Wolbachia* drug target. Recently, *Wolbachia* lipoprotein biosynthesis has been proposed as a potential chemotherapeutic target. Globomycin, a signal peptidase II inhibitor, was found to inhibit *Ehrlichia chaffeensis* infection and lipoprotein processing in cell cultures. [94] Globomycin was also obtained from the anti-*Wolbachial* drug screening project, and the result shows that this drug could deplete *Wolbachia* numbers in *Wolbachia*-containing *Ae. albopictus* cell line. In addition, Globomycin treatment could reduce motility and viability of *B. malayi* adult females *in vitro.* [88]

Moreover, a discovery of anti-*Wolbachial* drug and development program (A-WOL) has been established. This program tries to discover *Wolbachia* drug targets using bioinformatics tool and high-throughput screening approaches, to test antibiotic combinations for reduction of anti-*Wolbachial* treatment time, and to identify novel antibiotics over the currently used antibiotics. About 166 from 3,700 drugs have been filtered for in vivo screening to deliver increased property over doxycycline. [95]

Future directions

Wolbachia of arthropods and filarial nematodes have been extensively studied. For insect *Wolbachia*, studies such as, *Wolbachia*/host protein interactions at the molecular level [96], insect pest population control and desirable genotypes of arthropod populations spreading using *Wolbachia*-induced cytoplasmic incompatibility, and age-

modified vector populations are needed. [97, 98] *Wolbachia* was found to be of medical and veterinary importance for biological fight against vector-borne diseases. *Wolbachia* could be used for population replacement and suppression of mosquito vectors such as *Ae. aegypti* that transmits dengue and yellow fever, *Culex pipiens* that transmits West Nile virus, and *Anopheles* spp. that acts as the vectors for malaria. [28, 99] Recently, *Wolbachia* lipoprotein was found to be able to stimulate the inflammatory activity and disease symptom. Moreover, the lipid II biosynthesis pathway was identified to be necessary for *Wolbachia* cell division. It could be used as an anti-*Wolbachia* target for filarial infections. [100] Further investigations of host-filarial nematode-*Wolbachia* interactions, a much shorter regimen, drug combination, and registered drugs that could inhibit key biochemical pathway in the *Wolbachia* should be studied for anti-*Wolbachia* and anti-filarial activities in controlling filariasis.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง **"แบคทีเรียโวลบาเชียของแมลงและพยาธิกลุ่มฟิลาเรีย: ชีววิทยาและการประยุกต์"** โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก http://www.ccme.or.th

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คำถาม - คำตอบ

1. ข้อใดไม่ใช่ผลจากบทบาทหน้าที่ของแบคทีเรียโวลบาเชีย ที่มีต่อการควบคุมการสืบพันธุ์ของสัตว์ขาปล้อง
   - ก. cytoplasmic incompatibility
   - ข. mutualism
   - ค. feminization
   - ง. parthenogenesis
2. ข้อใดเป็นการศึกษาการใช้ประโยชน์จากแบคทีเรียโวลบาเชียในการควบคุมโรคที่นำโดยแมลงพาหะ
   - ก. dengue fever blocking transmission
   - ข. malaria blocking transmission
   - ค. west nile fever blocking transmission
   - ง. ถูกทุกข้อ
3. พยาธิฟิลาเรียชนิดใดที่ไม่พบแบคทีเรียโวลบาเชีย
   - ก. *Brugia malayi*
   - ข. *Wuchereria bancrofti*
   - ค. *Dirofilaria immitis*
   - ง. *Onchocerca flexuosa*

✂.....

คำตอบ สำหรับบทความเรื่อง **"แบคทีเรียโวลบาเชียของแมลงและพยาธิกลุ่มฟิลาเรีย: ชีววิทยาและการประยุกต์"**

จุฬาลงกรณ์เวชสาร ปีที่ 54 ฉบับที่ 6 เดือนพฤศจิกายน พ.ศ. 2553

รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/1011-(1003)

ชื่อ - นามสกุลผู้ขอ CME credit ..... เลขที่ใบประกอบวิชาชีพเวชกรรม.....

ที่อยู่.....

1. (ก) (ข) (ค) (ง)
2. (ก) (ข) (ค) (ง)
3. (ก) (ข) (ค) (ง)
4. (ก) (ข) (ค) (ง)
5. (ก) (ข) (ค) (ง)

4. ยาชนิดใดที่นำมาศึกษาทดลองในการรักษาผู้ป่วยจากพยาธิฟิลาเรีย

ก. rifampicin และ doxycycline

ข. doxycycline และ tigecycline

ค. rifampicin และ tetracycline

ง. tigecycline และ tetracycline

5. เอนไซม์อะไรของแบคทีเรียโวลบาเชีย ที่มีการศึกษาเพื่อนำมาใช้เป็นเป้าหมายของยา

ก. phosphoenolpyruvate

ข. pyruvate phosphate dikinase

ค. pyruvate kinase

ง. phosphofructokinase

เฉลย สำหรับบทความ รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/1009-(1002)

1. ง 2. ค 3. ค 4. ก 5. จ

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหน้า

ศาสตราจารย์นายแพทย์สุทธิพร จิตต์มิตรภาพ
ประธานคณะกรรมการการศึกษาต่อเนื่อง
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