

11-1-2010

Wolbachia of arthropods and filarial nematodes:biology and applications

S Sungpradit

S. Nuchprayoon

Follow this and additional works at: <https://digital.car.chula.ac.th/clmjjournal>



Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Sungpradit, S and Nuchprayoon, S. (2010) "Wolbachia of arthropods and filarial nematodes:biology and applications," *Chulalongkorn Medical Journal*: Vol. 54: Iss. 6, Article 7.

Available at: <https://digital.car.chula.ac.th/clmjjournal/vol54/iss6/7>

This Review Article is brought to you for free and open access by the Chulalongkorn Journal Online (CUJO) at Chula Digital Collections. It has been accepted for inclusion in Chulalongkorn Medical Journal by an authorized editor of Chula Digital Collections. For more information, please contact ChulaDC@car.chula.ac.th.

***Wolbachia* of arthropods and filarial nematodes: biology and applications**

Sivapong Sungpradit^{*,*}

Surang Nuchprayoon^{*}

Sungpradit S, Nuchprayoon S. *Wolbachia* of arthropods and filarial nematodes: biology and applications. Chula Med J 2010 Nov - Dec; 54(6): 605 - 21

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.

Reprint request: Nuchprayoon S. Lymphatic Filariasis Research Unit, Department of Parasitology, and Chulalongkorn Medical Research Center, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

E-mail: fmedstt@gmail.com

Received for publication. December 16, 2010.

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.

* Lymphatic Filariasis Research Unit, Department of Parasitology, and Chulalongkorn Medical Research Center, Faculty of Medicine, Chulalongkorn University

** Department of Pre-clinic and Applied Animal Science, Faculty of Veterinary Science, Mahidol University

**ศิวะพงษ์ สังข์ประดิษฐ์, สุรางค์ นุชประยูร. แบททีเรียโวลบาเซียของแมลงและพยาธิ
กลุ่มฟิลาเรีย: ชีววิทยาและการประยุกต์. จุฬาลงกรณ์เวชสาร 2553 พ.ย. - ธ.ค.; 54(6):
605 - 21**

โวลบาเซียเป็นกลุ่มแบคทีเรียชนิดแกรมลบที่ต้องอาศัยอยู่ในเซลล์ แบคทีเรียชนิดนี้มีบทบาท
หน้าที่เกี่ยวข้องกับการควบคุมการสืบพันธุ์ของสัตว์ขาปล้องหลายชนิด รวมถึงการพัฒนาของเอ็มบริโอ
และตัวอ่อนของพยาธิ การเจริญพันธุ์ของพยาธิเพศเมีย และการมีชีวิตรอดของพยาธิกลุ่มฟิลาเรีย
การศึกษาชีววิทยาประยุกต์ของแบคทีเรียโวลบาเซียสามารถนำมาดัดแปลงคุณสมบัติของแมลงศัตรูพืช
และแมลงนำโรค เพื่อลดหรือปรับเปลี่ยนจำนวนประชากรของแมลงดังกล่าวในธรรมชาติ นอกจากนี้
แบคทีเรียโวลบาเซียยังเป็นเป้าหมายใหม่ในการควบคุมโรคที่เกิดจากพยาธิกลุ่มฟิลาเรีย ในบทความนี้
นำเสนอชีววิทยาของแบคทีเรียโวลบาเซียในสัตว์ขาปล้องและพยาธิกลุ่มฟิลาเรีย รวมทั้งความก้าวหน้า
และทิศทางของการศึกษาวิจัย ได้แก่ การใช้แบคทีเรียโวลบาเซียในการเป็นเป้าหมาย เพื่อควบคุม
แมลงพาหะและการพัฒนายารักษาโรคที่เกิดจากพยาธิกลุ่มฟิลาเรีย

คำสำคัญ : แบคทีเรียโวลบาเซีย, 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 (*Kaloterme 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* (wMelPop) 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 similis*, and is designated to the supergroup I. So far, the molecular functions of *Wolbachia* 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 Dirofilarinae, 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 Dirofilarinae (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 <i>Wolbachia</i>	
			Positive	Negative
Filariidae	Filarinae	1	-	1
Onchocercidae	Onchocercinae	8	5	3
	Dirofilarinae	3	1	2
	Waltonellinae	1	-	1
	Setarinae	1	-	1
	Oswaldofilarinae	1	-	1
	Icosiellinae	0		
	Splendidofilarinae	0		
	Lemdaninae	0		

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

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

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/Dirofilarinae, 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/Dirofilarinae; 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* (wBm) 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 wBm 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 glycylicycline 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 wBm 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 wBm 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 wBm-PPDK and wBm-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.

Acknowledgement

We would like to thank Dr. Chantima Porksakorn for her helpful information and Venerable Dr. Mano Mettanando Laohavanich of the Foundation of King Rama IX, for editing the manuscript.

References

1. Werren JH. Biology of *Wolbachia*. *Annu Rev Entomol* 1997 Jan; 42: 587-609
2. Werren JH, Baldo L, Clark ME. *Wolbachia*: master manipulators of invertebrate biology. *Nat Rev Microbiol* 2008 Oct; 6(10): 741-51
3. Bandi C, Anderson TJ, Genchi C, Blaxter ML. Phylogeny of *Wolbachia* in filarial nematodes. *Proc Biol Sci* 1998 Dec 22; 265(1413): 2407-13
4. Dumler JS, Barbet AF, Bekker CP, Dasch GA, Palmer GH, Ray SC, Rikihisa Y, Rurangirwa FR. Reorganization of genera in the families *Rickettsiaceae* and *Anaplasmataceae* in the order Rickettsiales: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and 'HGE agent' as subjective synonyms of *Ehrlichia phagocytophila*. *Int J Syst Evol Microbiol* 2001 Nov; 51 Pt(6): 2145-65
5. Kocan KM, de la Fuente J, Blouin EF, Garcia-Garcia JC. *Anaplasma marginale* (Rickettsiales: Anaplasmataceae): recent advances in defining host-pathogen adaptations of a tick-borne rickettsia. *Parasitology* 2004; 129 Suppl: S285-300
6. Lo N, Casiraghi M, Salati E, Bazzocchi C, Bandi C. How many *Wolbachia* supergroups exist? *Mol Biol Evol* 2002 Mar; 19(3): 341-6
7. Zhou W, Rousset F, O'Neil S. Phylogeny and PCR-based classification of *Wolbachia* strains using *wsp* gene sequences. *Proc Biol Sci* 1998 Mar 22; 265(1395): 509-15
8. Bordenstein S, Rosengaus RB. Discovery of a novel *Wolbachia* supergroup in Isoptera. *Curr Microbiol* 2005 Dec; 51(6): 393-8
9. Vandekerckhove TT, Watteyne S, Willems A, Swings JG, Mertens J, Gillis M. Phylogenetic analysis of the 16S rDNA of the cytoplasmic bacterium *Wolbachia* from the novel host *Folsomia candida* (Hexapoda, Collembola) and its

- implications for wolbachial taxonomy. FEMS Microbiol Lett 1999 Nov 15; 180(2): 279-86
10. Lo N, Paraskevopoulos C, Bourtzis K, O'Neill SL, Werren JH, Bordenstein SR, Bandi C. Taxonomic status of the intracellular bacterium *Wolbachia pipientis*. Int J Syst Evol Microbiol 2007 Mar; 57 Pt(3): 654-7
 11. Rowley SM, Raven RJ, McGraw EA. *Wolbachia pipientis* in Australian spiders. Curr Microbiol 2004 Sep; 49(3): 208-14
 12. Ros VI, Fleming VM, Feil EJ, Breeuwer JA. How diverse is the genus *Wolbachia*? Multiple-gene sequencing reveals a putatively new *Wolbachia* supergroup recovered from spider mites (Acari: Tetranychidae). Appl Environ Microbiol 2009 Feb; 75(4): 1036-43
 13. Hertig, M. and S. B. Wolbach. Studies on rickettsia-like micro-organisms in insects. J Med Res 1924; 44: 329-74
 14. O'Neill SL, Giordano R, Colbert AM, Karr TL, Robertson HM. 16S rRNA phylogenetic analysis of the bacterial endosymbionts associated with cytoplasmic incompatibility in insects. Proc Natl Acad Sci USA 1992 Apr 1; 89(7): 2699-702
 15. Rousset F, Bouchon D, Pintureau B, Juchault P, Solignac M. *Wolbachia* endosymbionts responsible for various alterations of sexuality in arthropods. Proc Biol Sci 1992 Nov 23; 250(1328): 91-8
 16. Haine ER, Cook JM. Convergent incidences of *Wolbachia* infection in fig wasp communities from two continents. Proc Biol Sci 2005 Feb; 272(1561): 421-9
 17. Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH. How many species are infected with *Wolbachia*?—A statistical analysis of current data. FEMS Microbiol Lett 2008 Apr; 281(2): 215-20
 18. Bandi C, Dunn AM, Hurst GD, Rigaud T. Inherited microorganisms, sex-specific virulence and reproductive parasitism. Trends Parasitol 2001a Feb; 17(2): 88-94
 19. Stouthamer R, Breeuwer JA, Hurst GD. *Wolbachia pipientis*: microbial manipulator of arthropod reproduction. Annu Rev Microbiol 1999; 53: 71-102
 20. Sinkins SP. *Wolbachia* and cytoplasmic incompatibility in mosquitoes. Insect Biochem Mol Biol 2004 Jul; 34(7): 723-9
 21. McGraw EA, O'Neill SL. *Wolbachia pipientis*: intracellular infection and pathogenesis in *Drosophila*. Curr Opin Microbiol 2004 Feb; 7(1): 67-70
 22. Mercot H, Charlat S. *Wolbachia* infections in *Drosophila melanogaster* and *D. simulans*: polymorphism and levels of cytoplasmic incompatibility. Genetica 2004 Mar; 120(1-3): 51-9
 23. Huigens ME, Luck RF, Klaassen RH, Maas MF, Timmermans MJ, Stouthamer R. Infectious parthenogenesis. Nature 2000 May; 405(6783): 178-9
 24. Huigens ME, de Almeida RP, Boons PA, Luck RF, Stouthamer R. Natural interspecific and intraspecific horizontal transfer of parthenogenesis-inducing *Wolbachia* in *Trichogramma* wasps. Proc Biol Sci 2004 Mar; 271(1538): 509-15
 25. Moreau J, Rigaud T. Variable male potential rate

- of reproduction: high male mating capacity as an adaptation to parasite-induced excess of females? *Proc Biol Sci* 2003 Jul 22; 270(1523): 1535-40
26. Cordaux R, Michel-Salzat A, Frelon-Raimond M, Rigaud T, Bouchon D. Evidence for a new feminizing *Wolbachia* strain in the isopod *Armadillidium vulgare*: evolutionary implications. *Heredity* 2004 Jul; 93(1): 78-84
27. Beard CB, O'Neill SL, Tesh RB, Richards FF, Aksoy S. Modification of arthropod vector competence via symbiotic bacteria. *Parasitol Today* 1993 May; 9(5): 179-83
28. McMeniman CJ, Lane RV, Cass BN, Fong AW, Sidhu M, Wang YF, O'Neill SL. Stable introduction of a life-shortening *Wolbachia* infection into the mosquito *Aedes aegypti*. *Science* 2009 Jan 2; 323(5910): 141-4
29. Sinkins SP, Gould F. Gene drive systems for insect disease vectors. *Nat Rev Genet* 2006 Jun; 7(6): 427-35
30. McGraw EA, O'Neill SL. Evolution of *Wolbachia pipientis* transmission dynamics in insects. *Trends Microbiol* 1999 Jul; 7(7): 297-302
31. Townson H. *Wolbachia* as a potential tool for suppressing filarial transmission. *Ann Trop Med Parasitol* 2002 Dec; 96 Suppl 2: S117-27
32. Hotopp JC, Clark ME, Oliveira DC, Foster JM, Fischer P, Torres MC, Giebel JD, Kumar N, Ishmael N, Wang S, et al. Widespread lateral gene transfer from intracellular bacteria to multicellular eukaryotes. *Science* 2007 Sep; 317(5845): 1753-6
33. Blaxter M. Symbiont genes in host genomes: fragments with a future? *Cell Host Microbe* 2007 Oct; 2(4): 211-3
34. Nikoh N, Tanaka K, Shibata F, Kondo N, Hizume M, Shimada M, Fukatsu T. *Wolbachia* genome integrated in an insect chromosome: evolution and fate of laterally transferred endosymbiont genes. *Genome Res* 2008 Feb; 18(2): 272-80
35. Kondo N, Nikoh N, Ijichi N, Shimada M, Fukatsu T. Genome fragment of *Wolbachia* endosymbiont transferred to X chromosome of host insect. *Proc Natl Acad Sci USA* 2002 Oct; 99(22): 14280-5
36. Fenn K, Conlon C, Jones M, Quail MA, Holroyd NE, Parkhill J, Blaxter M. Phylogenetic relationships of the *Wolbachia* of nematodes and arthropods. *PLoS Pathog* 2006 Oct; 2(10): e94
37. Mitreva M, Smart G, Helder J. Role of horizontal gene transfer in the evolution of plant parasitism among nematodes. *Methods Mol Biol* 2009; 532: 517-35
38. Lee CC. *Dirofilaria immitis*: ultrastructural aspects of oocyte development and zygote formation. *Exp Parasitol* 1975 Jun; 37(3): 449-68
39. McLaren DJ, Worms MJ, Laurence BR, Simpson MG. Micro-organisms in filarial larvae (Nematoda). *Trans R Soc Trop Med Hyg* 1975; 69(5-6): 509-14
40. Kozek WJ. Transovarially-transmitted intracellular microorganisms in adult and larval stages of *Brugia malayi*. *J Parasitol* 1977 Dec; 63(6): 992-1000
41. Kozek WJ, Marroquin HF. Intracytoplasmic bacteria in *Onchocerca volvulus*. *Am J Trop*

- Med Hyg 1977 Jul; 26(4): 663-78
42. Sironi M, Bandi C, Sacchi L, Di Sacco B, Damiani G, Genchi C. Molecular evidence for a close relative of the arthropod endosymbiont *Wolbachia* in a filarial worm. *Mol Biochem Parasitol* 1995 Nov; 74(2): 223-7
 43. McGarry HF, Egerton GL, Taylor MJ. Population dynamics of *Wolbachia* bacterial endosymbionts in *Brugia malayi*. *Mol Biochem Parasitol* 2004 May; 135(1): 57-67
 44. Fenn K, Blaxter M. Quantification of *Wolbachia* bacteria in *Brugia malayi* through the nematode life cycle. *Mol Biochem Parasitol* 2004 Oct; 137(2): 361-4
 45. Sacchi L, Corona S, Casiraghi M, Bandi C. Does fertilization in the filarial nematode *Dirofilaria immitis* occur through endocytosis of spermatozoa? *Parasitology* 2002 Jan; 124 Pt(1): 87-95
 46. Kozek WJ. What is new in the *Wolbachia/Dirofilaria* interaction? *Vet Parasitol* 2005 Oct; 133(2-3): 127-32
 47. Henkle-Dührsen K, Eckelt VH, Wildenburg G, Blaxter M, Walter RD. Gene structure, activity and localization of a catalase from intracellular bacteria in *Onchocerca volvulus*. *Mol Biochem Parasitol* 1998 Oct 30; 96(1-2): 69-81
 48. Fischer P, Wibowo H, Pischke S, Rückert P, Liebau E, Ismid IS, Supali T. PCR-based detection and identification of the filarial parasite *Brugia timori* from Alor Island, Indonesia. *Ann Trop Med Parasitol* 2002 Dec; 96(8): 809-21
 49. Egyed Z, Sréter T, Széll Z, Nyiro G, Márialigeti K, Varga I. Molecular phylogenetic analysis of *Onchocerca lupi* and its *Wolbachia* endosymbiont. *Vet Parasitol* 2002 Sep 10; 108(2): 153-61
 50. Grobusch MP, Kombila M, Autenrieth I, Mehlhorn H, Kreamsner PG. No evidence of *Wolbachia* endosymbiosis with *Loa loa* and *Mansonella perstans*. *Parasitol Res* 2003 Aug; 90(5): 405-8
 51. Casiraghi M, Bain O, Guerrero R, Martin C, Pocacqua V, Gardner SL, Franceschi A, Bandi C. Mapping the presence of *Wolbachia pipientis* on the phylogeny of filarial nematodes: evidence for symbiont loss during evolution. *Int J Parasitol* 2004 Feb; 34(2): 191-203
 52. Bain O, Casiraghi M, Martin C, Uni S. The nematoda Filarioidea: critical analysis linking molecular and traditional approaches. *Parasite* 2008 Sep; 15(3): 342-8
 53. Haegeman A, Vanholme B, Jacob J, Vandekerckhove TT, Claeys M, Borgonie G, Gheysen G. An endosymbiotic bacterium in a plant-parasitic nematode: Member of a new *Wolbachia* supergroup. *Int J Parasitol* 2009 Jul 15; 39(9): 1045-54
 54. Plenge-Bönig A, Krömer M, Büttner DW. Light and electron microscopy studies on *Onchocerca jakutensis* and *O. flexuosa* of red deer show different host-parasite interactions. *Parasitol Res* 1995; 81(1): 66-73
 55. Casiraghi M, Anderson TJ, Bandi C, Bazzocchi C, Genchi C. A phylogenetic analysis of filarial nematodes: comparison with the phylogeny of *Wolbachia* endosymbionts.

- Parasitology 2001 Jan; 122 Pt(1): 93-103
56. Büttner DW, Wanji S, Bazzocchi C, Bain O, Fischer P. Obligatory symbiotic *Wolbachia* endobacteria are absent from *Loa loa*. *Filaria J* 2003 May; 2(1): 10
 57. Bordenstein SR, Fitch DHA, Werren JH. Absence of *Wolbachia* in nonfilariid nematodes. *J Nematol* 2003 Sep; 35: 266-70
 58. Duron O, Gavotte L. Absence of *Wolbachia* in nonfilariid worms parasitizing arthropods. *Curr Microbiol* 2007 Sep; 55(3): 193-7
 59. Taylor MJ, Bandi C, Hoerauf A. *Wolbachia* bacterial endosymbionts of filarial nematodes. *Adv Parasitol* 2005a; 60: 245-84
 60. Bordenstein SR, Paraskevopoulos C, Hotopp JC, Sapountzis P, Lo N, Bandi C, Tettelin H, Werren JH, Bourtzis K. Parasitism and mutualism in *Wolbachia*: what the phylogenomic trees can and cannot say. *Mol Biol Evol* 2009 Jan; 26(1): 231-41
 61. Taylor MJ, Hoerauf A. *Wolbachia* bacteria of filarial nematodes. *Parasitol Today* 1999 Nov; 15(11): 437-42
 62. Taylor MJ, Bilo K, Cross HF, Archer JP, Underwood AP. 16S rDNA phylogeny and ultrastructural characterization of *Wolbachia* intracellular bacteria of the filarial nematodes *Brugia malayi*, *B. pahangi*, and *Wuchereria bancrofti*. *Exp Parasitol* 1999 Apr; 91(4): 356-61
 63. Higazi TB, Filiano A, Katholi CR, Dadzie Y, Remme JH, Unnasch TR. *Wolbachia* endosymbiont levels in severe and mild strains of *Onchocerca volvulus*. *Mol Biochem Parasitol* 2005 May; 141(1): 109-12
 64. Saint André A, Blackwell NM, Hall LR, Hoerauf A, Brattig NW, Volkmann L, Taylor MJ, Ford L, Hise AG, Lass JH, et al. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. *Science* 2002 Mar 8; 295(5561): 1892-5
 65. Johnston KL, Taylor MJ. *Wolbachia* in filarial parasites: targets for filarial infection and disease control. *Curr Infect Dis Rep* 2007 Jan; 9(1): 55-9
 66. Hise AG, Daehnel K, Gillette-Ferguson I, Cho E, McGarry HF, Taylor MJ, Golenbock DT, Fitzgerald KA, Kazura JW, Pearlman E. Innate immune responses to endosymbiotic *Wolbachia* bacteria in *Brugia malayi* and *Onchocerca volvulus* are dependent on TLR2, TLR6, MyD88, and Mal, but not TLR4, TRIF, or TRAM. *J Immunol* 2007 Jan 15; 178(2): 1068-76
 67. Turner JD, Langley RS, Johnston KL, Gentil K, Ford L, Wu B, Graham M, Sharples F, Slatko B, Pearlman E, Taylor MJ. *Wolbachia* lipoprotein stimulates innate and adaptive immunity through toll-like receptors 2 and 6 (TLR2/6) to induce disease manifestations of filariasis. *J Biol Chem*. 2009 May 19
 68. Foster J, Ganatra M, Kamal I, Ware J, Makarova K, Ivanova N, Bhattacharyya A, Kapatral V, Kumar S, Posfai J, et al. The *Wolbachia* genome of *Brugia malayi*: endosymbiont evolution within a human pathogenic nematode. *PLoS Biol* 2005 Apr; 3(4): e121
 69. Sun LV, Foster JM, Tzertzinis G, Ono M, Bandi C, Slatko BE, O'Neill SL. Determination of *Wolbachia* genome size by pulsed-field gel

- electrophoresis. *J Bacteriol* 2001 Apr; 183(7): 2219-25
70. Gómez-Valero L, Silva FJ, Christophe Simon J, Latorre A. Genome reduction of the aphid endosymbiont *Buchnera aphidicola* in a recent evolutionary time scale. *Gene* 2007 Mar 1; 389(1): 87-95
71. Moran NA, McLaughlin HJ, Sorek R. The dynamics and time scale of ongoing genomic erosion in symbiotic bacteria. *Science* 2009 Jan 16; 323(5912): 379-82
72. Masui S, Sasaki T, Ishikawa H. Genes for the type IV secretion system in an intracellular symbiont, *Wolbachia*, a causative agent of various sexual alterations in arthropods. *J Bacteriol* 2000 Nov; 182(22): 6529-31
73. Rancès E, Voronin D, Tran-Van V, Mavingui P. Genetic and functional characterization of the type IV secretion system in *Wolbachia*. *J Bacteriol* 2008 Jul; 190(14): 5020-30
74. Park J, Kim KJ, Choi KS, Grab DJ, Dumler JS. *Anaplasma phagocytophilum* AnkA binds to granulocyte DNA and nuclear proteins. *Cell Microbiol* 2004 Aug; 6(8): 743-51
75. Ijdo JW, Carlson AC, Kennedy EL. *Anaplasma phagocytophilum* AnkA is tyrosine-phosphorylated at EPIYA motifs and recruits SHP-1 during early infection. *Cell Microbiol* 2007 May; 9(5): 1284-96
76. Warbrick EV, Barker GC, Rees HH, Howells RE. The effect of invertebrate hormones and potential hormone inhibitors on the third larval moult of the filarial nematode, *Dirofilaria immitis*, *in vitro*. *Parasitology* 1993 Nov; 107 Pt(4): 459-63
77. Höss S, Weltje L. Endocrine disruption in nematodes: effects and mechanisms. *Ecotoxicology* 2007 Feb; 16(1): 15-28
78. Ghedin E, Wang S, Spiro D, Caler E, Zhao Q, Crabtree J, Allen JE, Delcher AL, Guiliano DB, Miranda-Saavedra D, et al. Draft genome of the filarial nematode parasite *Brugia malayi*. *Science* 2007 Sep 21; 317(5845): 1756-60
79. Ghedin E, Daehnel K, Foster J, Slatko B, Lustigman S. The symbiosis relationship between parasitic nematodes and their *Wolbachia* endosymbionts - A resource for a new generation of control measures. *Symbiosis* 2008; 46(2): 77-85
80. Ford L, Johnston KL, Ambrose PA, Draper MP, Bhatia B, Taylor MJ. A-*Wolbachia* drug discovery – screening of novel derivatives of tetracycline with improved efficacy over doxycycline in an *in vitro* *Wolbachia* cell-line assay. Program and abstract of the 57th annual meeting of American Society for Tropical Medicine and Hygiene (ASTMH) 2008; 79: 128
81. Bandi C, Trees AJ, Brattig NW. *Wolbachia* in filarial nematodes: evolutionary aspects and implications for the pathogenesis and treatment of filarial diseases. *Vet Parasitol* 2001b Jul 12; 98(1-3): 215-38
82. Hoerauf A. Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis. *Curr Opin Infect Dis* 2008 Dec; 21(6): 673-81
83. Turner JD, Mand S, Debrah AY, Muehlfeld J, Pfarr K, McGarry HF, Adjei O, Taylor MJ,

- Hoerauf A. A randomized, double-blind clinical trial of a 3-week course of doxycycline plus albendazole and ivermectin for the treatment of *Wuchereria bancrofti* infection. Clin Infect Dis 2006 Apr 15; 42(8): 1081-9
84. Debrah AY, Mand S, Marfo-Debrekeyei Y, Batsa L, Pfarr K, Buttner M, Adjei O, Buttner D, Hoerauf A. Macrofilaricidal effect of 4 weeks of treatment with doxycycline on *Wuchereria bancrofti*. Trop Med Int Health 2007 Dec; 12(12): 1433-41
85. Hoerauf A, Mand S, Fischer K, Kruppa T, Marfo-Debrekeyei Y, Debrah AY, Pfarr KM, Adjei O, Buttner DW. Doxycycline as a novel strategy against bancroftian filariasis-depletion of *Wolbachia* endosymbionts from *Wuchereria bancrofti* and stop of microfilaria production. Med Microbiol Immunol 2003 Nov; 192(4): 211-6
86. Supali T, Djuardi Y, Pfarr KM, Wibowo H, Taylor MJ, Hoerauf A, Houwing-Duistermaat JJ, Yazdanbakhsh M, Sartono E. Doxycycline treatment of *Brugia malayi*-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. Clin Infect Dis 2008 May 1; 46(9): 1385-93
87. Taylor MJ, Makunde WH, McGarry HF, Turner JD, Mand S, Hoerauf A. Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: a double-blind, randomised placebo-controlled trial. Lancet 2005b Jun 18-24; 365(9477): 2116-21
88. Johnston KL, Wu B, Guimaraes A, Ford L, Ambrose PA, Slatko BE, Taylor MJ. Globomycin: A new class of drug with efficacy against *Wolbachia* and filarial nematodes. Program and abstract of the 57th annual meeting of American Society for Tropical Medicine and Hygiene (ASTMH) 2008; 79: 128
89. Rao RU. Endosymbiotic *Wolbachia* of parasitic filarial nematodes as drug targets. Indian J Med Res 2005 Sep; 122(3): 199-204
90. Specht S, Mand S, Marfo-Debrekeyei Y, Debrah AY, Konadu P, Adjei O, Buttner DW, Hoerauf A. Efficacy of 2- and 4-week rifampicin treatment on the *Wolbachia* of *Onchocerca volvulus*. Parasitol Res 2008 Nov; 103(6): 1303-9
91. Raverdy S, Foster JM, Roopenian E, Carlow CK. The *Wolbachia* endosymbiont of *Brugia malayi* has an active pyruvate phosphate dikinase. Mol Biochem Parasitol 2008 Aug; 160(2): 163-6
92. Jedrzejewski MJ. Structure, function, and evolution of phosphoglycerate mutases: comparison with fructose-2,6-bisphosphatase, acid phosphatase, and alkaline phosphatase. Prog Biophys Mol Biol 2000; 73(2-4): 263-87
93. Foster JM, Raverdy S, Ganatra MB, Colussi PA, Taron CH, Carlow CK. The *Wolbachia* endosymbiont of *Brugia malayi* has an active phosphoglycerate mutase: a candidate target for anti-filarial therapies. Parasitol Res 2009 Apr; 104(5): 1047-52
94. Huang H, Lin M, Wang X, Kikuchi T, Mottaz H, Norbeck A, Rikihisa Y. Proteomic analysis of and immune responses to *Ehrlichia chaffeensis* lipoproteins. Infect Immun 2008 Aug; 76(8): 3405-14

95. Bockarie MJ, Taylor MJ, Gyapong JO. Current practices in the management of lymphatic filariasis. *Expert Rev Anti Infect Ther.* 2009 Jun;7(5):595-605.
96. Xi Z, Gavotte L, Xie Y, Dobson SL. Genome-wide analysis of the interaction between the endosymbiotic bacterium *Wolbachia* and its *Drosophila* host. *BMC Genomics* 2008 Jan 2; 9: 1
97. Serbus LR, Casper-Lindley C, Landmann F, Sullivan W. The genetics and cell biology of *Wolbachia*-host interactions. *Annu Rev Genet* 2008; 42: 683-707
98. Bourtzis K. *Wolbachia*-based technologies for insect pest population control. *Adv Exp Med Biol* 2008; 627: 104-13
99. Rasgon J. Population replacement strategies for controlling vector populations and the use of *Wolbachia pipiensis* for genetic drive. *J Vis Exp.* 2007; (5): 225
100. Henrichfreise B, Schiefer A, Schneider T, Nzukou E, Poellinger C, Hoffmann TJ, Johnston KL, Moelleken K, Wiedemann I, Pfarr K, Hoerauf A, Sahl HG. Functional conservation of the lipid II biosynthesis pathway in the cell wall-less bacteria *Chlamydia* and *Wolbachia*: why is lipid II needed? *Mol Microbiol* 2009 Sep; 73(5): 913-23

กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง “แบคทีเรียโวลบาเซียของแมลงและพยาธิกลุ่มฟีลาเรีย: ชีววิทยาและการประยุกต์” โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก <http://www.ccme.or.th>

คำถาม - คำตอบ

- ข้อใดไม่ใช่ผลจากบทบาทหน้าที่ของแบคทีเรียโวลบาเซีย ที่มีต่อการควบคุมการสืบพันธุ์ของสัตว์ขาปล้อง
 - cytoplasmic incompatibility
 - mutualism
 - feminization
 - parthenogenesis
- ข้อใดเป็นการศึกษาการให้ประโยชน์จากแบคทีเรียโวลบาเซียในการควบคุมโรคที่นำโดยแมลงพาหะ
 - dengue fever blocking transmission
 - malaria blocking transmission
 - west nile fever blocking transmission
 - ถูกทุกข้อ
- พยาธิฟีลาเรียชนิดใดที่ไม่พบแบคทีเรียโวลบาเซีย
 - Brugia malayi*
 - Wuchereria bancrofti*
 - Dirofilaria immitis*
 - Onchocerca flexuosa*

✂.....

คำตอบ สำหรับบทความเรื่อง “แบคทีเรียโวลบาเซียของแมลงและพยาธิกลุ่มฟีลาเรีย: 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)

4. (ก) (ข) (ค) (ง)

2. (ก) (ข) (ค) (ง)

5. (ก) (ข) (ค) (ง)

3. (ก) (ข) (ค) (ง)

4. ยาชนิดใดที่นำมาศึกษาทดลองในการรักษาผู้ป่วยจากพยาธิฟิลาเรีย
- ก. rifampicin และ doxycycline
 - ข. doxycycline และ tigecycline
 - ค. rifampicin และ tetracycline
 - ง. tigecycline และ tetracycline
5. เอนไซม์อะไรของแบคทีเรียไวลบาเซีย 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)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านล่าง

ศาสตราจารย์นายแพทย์สุทธิพร จิตต์มิตรภาพ
ประธานคณะกรรมการการศึกษาต่อเนื่อง
ตึกอำนวยการ ชั้น 5
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
เขตปทุมวัน กทม. 10330