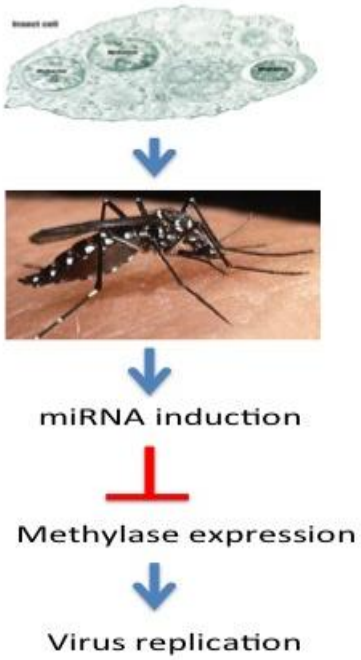
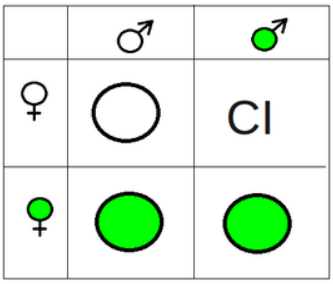
Wolbachia uses a host microRNA to regulate transcripts of a cytosine methyl-transferase, contributing to dengue virus inhibition in *Aedes aegypti*.

Zhang et al., PNAS 110, 10276-81, 2013

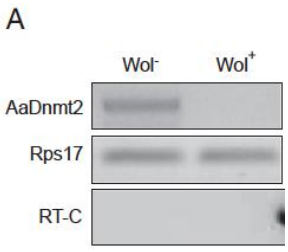


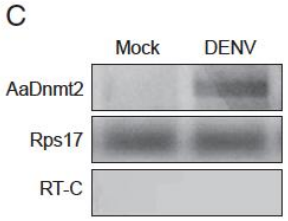
- *Wolbachia* is an obligate intracellular bacterium found in arthropods
- The presence of *Wolbachia* in insects diminishes the transmission of viruses and parasites
- *Wolbachia* induces a host mi-RNA, which reduces the expression of a cytosine DNA methylase required for Dengue virus replication
- Replication of Dengue virus can be rescued by preventing down-regulation of the methylase

• *Wolbachia* is a parasitic to endosymbiotic bacterium of arthropods. Its endosymbiontic life style is very successful and more than 40% of all insect species and 28% of mosquito species are infected. The bacteria are transmitted vertically by the females. Different mechanisms including male killing, feminization, parthenogenesis, and cytoplasmic incompatibility (CI) are used to invade successfully a host. In CI the offspring of infected females and infected or uninfected males are viable, but those from infected males with uninfected females are embryonic lethal (4). The CI involves a defect in chromosome condensation and cytokinesis of the parental chromosomes (2). This modification is induced by *Wolbachia*, but occurs in absence of the bacterium, since bacteria are no longer present in the sperm. An unknown rescue factor present in the infected female allows a successful first mitosis to occur. Thereby, in a laboratory experiment where 50 females and 50 males were mixed with 5% of infected females, within 8 generations, 100% of the mosquitos *Anopheles stephensi* were infected (1).

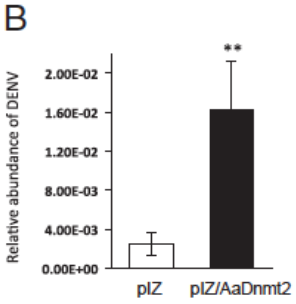


• Interestingly *Wolbachia* induces pathogen interference (PI) that could be explained by increased immune state of the host or by resource competition, but can also – depending on the bacterial strain and the host – induce drastic lifespan shortening of the host (3). It has been shown previously that artificially Wolbachia-infected Anopheles show a reduction of *Plasmodium falciparum* oocyst levels in the insect midgut. Although Anopheles are not natural hosts for Wolbachia, a recent report showed establishment of Wolbachia in *Anopheles stephensi* (1). Other reports show PI with Dengue, yellow fever, and Chikungunya, viruses that are transmitted by insects.





• Reports have shown that *Wolbachia* induces the up-regulation in *Aedes aegypti* of a host miRNA (miR-2940) that is required for the upregulation of a host-metalloprotease, required for maintenance of the bacteria (Zhang *et al*.). This insect is also an important host for Dengue virus (DENV) and it has been reported that *Wolbachia* infected *Ae. aegypti* insects are resistant to DENV infection. In contrast to the upregulation of the host-metalloprotease, the recent report by Zhang *et al*., shows a reduction of the expression of *Dnmt2* gene, encoding a 5'-cytosine DNA methylase. Importantly, DENV infected insects show an increased expression of Dnmt2 and its mRNA was predicted to be a target of the same miRNA miR-2940.



Whereas overexpression of Dnmt2 reduces the level of bacteria in insect cells and DENV levels were much higher in Dnmt2 overexpressing cells, DENV replication was not enhanced in *Wolbachia* infected cells, consistent with the pathogen interference suppressing virus replication in Wolbachia-infected insects. Importantly, in *Wolbachia* infected cells expressing a miR-2940-inhibitor, DENV replication is restored.

(1) Bian et al., Science 340, 748-541, 2013; (2) Serbus et al., Annu. Rev. Genet. 2008. 42:683–707; (3) Hughes et al., PLoS Pathog 7(5): e1002043. , (4) http://en.wikipedia.org/wiki/Cytoplasmic_incompatibility