# Immunity-Reproduction Trade-off Conflict and the Battle Against Malaria

## I- Originality

Because of the resistance of *Plasmodium* and mosquitoes to drugs and insecticides respectively, the recent alternative for controlling malaria is genetically modifying the vector to become incompetent for transmitting this disease. On this behalf, the two main recently suggested malaria control strategies are: **a)** utilizing the immune system of the vector to kill the malaria parasite (Kokoza *et al.,* 2000), and **b)** the malaria transmission-blocking strategy *via* interrupting the malaria life cycle at the midgut level (Yoshida *et al*., 2001) and/or at the salivary gland level (Yoshida, personal communication). In fact, the immune system is very effective against malaria parasite in the refractory mosquitoes (Collins *et al.*, 1986; and Paskewitz *et al*., 1989). Based on these researches, scientists have raised the suggestion that susceptible mosquitoes could be genetically modified to become incompetent for transmitting malaria *via* one or both of the above mentioned strategies.

## II- Importance

The criticism here is that if mosquito transgenesis strategy that aiming to utilizing the immune system of the malaria vector against malaria is adopted, the genetically modified mosquitoes might pay a price in terms of reduced reproductive fitness (immunity reproduction trade-off) (Moret and Schmid-Hempel, 2000). This, in fact, could significantly limit this strategy. Thus, the hypothesis of my work is to explore the impact of both malaria infection and immune induction on the reproductive fitness of the African malaria vector, *Anopheles gambiae*.

First, it has been explored that infection with *Plasmodium yoelii nigeriensis* has significantly reduced the fecundity (total number of eggs produced/female) of *An. gambiae* by 41.2% (Ahmed *et al*., 1999) compared to non-infected mosquitoes. The mechanism behind this reduction was studied and found to occur *via* affecting most of the vitellogenesis aspects. On one hand, vitellogenin mRNA abundance in the fat body, vitellogenin (Vg) titre in the haemolymph and vitellin (Vn) content in the ovary were significantly reduced malaria infected mosquitoes (Ahmed *et al*., 2001). On the other hand, percentages of follicular resorption and apoptosis were significantly increased in the ovaries of infected mosquitoes (Hopwood *et al*., 2002). And consequently, the Vg uptake functional machinery of the ovary was significantly affected. These studies may explain the mechanism behind fecundity reduction as a result of malaria infection. This in fact, may indicate a significant limitation of the immuno-engineered mosquito strategy that explored by Alex Raikhel and co-workers (Kokoza *et al.,* 2000) as they are mainly relying upon using the Vg gene as the promoter for the defensin (the candidate gene) in inducing the vector systemic immunity against malaria.

Second, it has been suggested that the main effect of parasitic infection is by the costs imposed when the host immune system is activated (Moret and Schmid-Hempel, 2000). Furthermore, natural refractoriness of mosquito to *Plasmodium* has also been proven to be very costly **(**Ferdig, *et al*., 1993 and Yan *et al.*, 1997**)**. Thus, it was important to test the hypothesis that enforcing the immune system to work efficiently against *Plasmodium* malaria could be costly in terms of reproductive success. Thus, when the immune system of blood-fed mosquitoes was stimulated by injecting lipopolysaccharide (LPS) resulted in a concomitant significant reduction in the ovarian Vn content, and hence, fecundity was significantly reduced (Ahmed *et al.*, 2002). These findings raised the question whether or not this impact on fecundity may have occurred *via* the same mechanism in malaria-infected mosquitoes. Thus, the reproductive cost of mounting the two main effective immune responses against *Plasmodium* (melanization and humoral responses) was explored in my very recent studies. It has been shown that induction of humoral antibacterial activity and melanization response have resulted in a significant 257.7% and 134.37% increase respectively in follicular apoptosis (Ahmed and Hurd, 2005). Moreover, as the process of follicular apoptosis proceeds follicular resorption, the later has also been found to be significantly increased as a result of melanization and humoral antibacterial activity (Ahmed, 2005a & b). Thus, immune induction has significantly reduced vector fecundity in the same mechanism as in malaria infection.

## II- Significance

These findings raise up a warning message as that care should be taken while thing about utilizing the immune system of the vector in the battle against malaria. On the other hand, it is not known whether or not the second strategy, (transmission-blocking strategy) affects the reproductive fitness of the modified mosquitoes. Thus, it is of interest to establish whether or not this strategy affects fecundity of the modified mosquito which may help in winning the battle against malaria.

The recent ongoing work is going in collaboration with the malaria group at Keele University, UK (for more details, please see: www.keele.ac.uk/depts/aep/collab/aa.htm).

## References


**Ahmed, A. M.**, Maingon, Taylor, R. D. P. J. and Hurd, H. (1999). The effect of infection with *Plasmodium yoelii nigeriensis* on the reproductive fitness of the mosquito *Anopheles gambiae. Invertebrate Reproduction and Development*. **36**: 217-222.

**Ahmed, A. M.**, Rhayza, M., Romans, P., and Hurd, H. (2001). Effects of malaria infection on vitellogenesis in *Anopheles gambiae* during tow gonotrophic cycles. *Insect Molecular Biology*. **10(4)**: 347-356.

**Ahmed, A. M.,** Baggott, S.**,** Maingon, R. and Hurd, H. (2002). The costs of mounting an immune response are reflected in the reproductive fitness of the mosquito *Anopheles gambiae. OIKOS* **97:** 371–377.

**Ahmed, A. M.** (2004). Activation of the immune system of *Anopheles gambiae* against malaria parasite: a comparison between bacterial infection and a botanical extract. *The 3rd International Conference on Biological Science. University of Tanta, Tanta, EGYPT, 28 – 29 April. Proc. I.C.B.S.*, **3(1)**: 122 - 141

**Ahmed, A. M.** (2005*a*). Melanization of sephadex beads by the malaria vector, *anopheles gambiae*: effect of blood meal, and mechanisms of reproductive costs**.** *The Egyptian German Society of Zoology*. **47(A)**: In Press.

**Ahmed, A. M.** (2005*b*). The humoral anti-bacterial response of *Anopheles gambiae* and the immunity-reproduction trade-off: between the hope and limitation of the malaria immuno-control strategy. *The 3rd International Conference of Applied Entomology, Cairo University* (In Press).

**Ahmed, A. M.** and Hurd, H (2005)**.** Immune stimulation and malaria infection impose reproductive costs in *Anopheles gambiae via* follicular apoptosis. *Microbes and Infection* (In Press).

Collins, F. H., Sakai, R. K., Vernick, K. D., Paskewitz, S. Seeley, D. C., Miller, L. H., Collins, W. E., Campbell, C. C. and Gwadz, R. W. (1986). Genetic selection of a *Plasmodium*-refractory strain of the malaria vector *Anopheles gambiae. Science.* **234**: 607-610.

Ferdig, M. T., Beemtsen, B. T., Spray, F. J., Jianyong, L. and Christensen, B. M. (1993). Reproductive costs associated with resistenc in a mosquito-filarial worm system. *American Journal of Tropical Medicine and Hygiene.* **49:** 756-762.

Hopwood, J. A., **Ahmed, A. M**., Polwart, A., Williams, G. T. and Hurd, H. (2001). Malaria-induced apoptosis in mosquito ovaries: a mechanism to control vector egg production. *The Journal of Experimental Biology*. 204: 2773-2780.

Kokoza, V., Ahmed, A., Cho, W-L, Jasinskiene, N., James, A. A. and Raikhel, A. (2000). Engineering blood meal-activated systemic immunity in the yellow fever mosquito, *Aedes aegypti. Proceedings of the National Academy of Science of America, USA.* **97**: 9144-9149.

Moret, Y. and Schmid-Hempel, P. (2000). Survival for immunity: the price of immune system activation for bumblebee workers. *Science*. **290**: 1166-1168.

Paskewitz, S. M., Brown, M. R., Collins, F. H. and Lea, A. O. (1989). Ultrastructural localization of phenoloxidase in the midgut of refractory *Anopheles gambiae* and association of the enzyme with encapsulated *Plasmodium cynmolgi. Parasitology.* **75**: 594-600.

Shahabuddin, M, Fields, I., Bulet, P., Hoffman, J. A. and Miller, L. H. (1998) *Plasmodium gallinaceum* differential killing of some mosquito stages of the parasite by insect defensin. *Experimental Parasitology.* **89**: 103-112.

Yan, G., Severson, D. W. and Christensen, B. M. (1997). Costs and benefits of mosquito refractoriness to malaria parasites: implications for genetic variability of mosquitoes and genetic control of malaria. *Evolution.* **51 (2)**: 441-450.

Yoshida, S., Ioka, D., Matsuoka, H., Endo, H. and Ishii, A. (2001). Bacteria expressing single-chain immunotoxin inhibit malaria parasite development in mosquitoes. *Molecular and Biochemical Parasitology*. **113**: 89-96.